GABA Uptake Inhibitors Having A Pyrrolidine Structure

Description

This application is a 371 of PCT/EP99/06486 09/03/1999.

The present invention relates to GABA uptake inhibitors having a pyrrolidine structure. The present invention further relates to pharmaceutical compositions containing such compounds, as well as to the use of these compounds for the treatment of disorders of the central nervous system (CNS) in which GABA uptake inhibitors play a role, e.g., epilepsy and Chorea Huntington.

With about 50 million affected patients, epilepsy is still one of the most common brain disorders. Due to the large variety of seizure forms and a still present lack of aetiological understanding, to date therapy approaches are limited to controlling the symptoms, e.g., suppressing epileptic fits.

The rudiments of modern therapy go back to the middle of the last century, where bromides were proposed for the treatment of epileptics. It was only in 1912 when the anticonvulsive activity of phenobarbital was discovered. Soon thereafter the first hydantoin derivative was used as antiepileptic. Like phenobarbital, phenytoin, a hydantoin derivative which was introduced in 1938, is still on the market today and is used with Grand Mal, a primarily generalized seizure form of epilepsy.

In the late 60'ies the list of antiepileptics was extended by the group of the benzodiazepines, examples whereof are diazepam and clonazepam.

The mechanisms of action of the individual representatives vary strongly. It did turn out, however, that the γ-aminobutyric acid (GABA)-mediated inhibition of excitation transmission is a primary starting point.

After almost one century of a purely empirical development of the antiepileptics, methods for the purposive development of antiepileptics arose only in the last two decades when people started to understand the molecularbiological context.

In the 50'ies the discovery of GABA in the brains of mammals was reported, without understanding, however, the function thereof. At that time it was presumed for the first time that GABA possibly functions as an inhibitor in the CNS. In 1971 it was finally possible to detect the presence of GABA receptors. Today one distinguishes between $GABA_A$ and $GABA_B$ receptors, and in the meantime it has been found out that the $GABA_A$ receptor is a ion channel protein which is composed of various subunits.

Already in 1968 a high affinity GABA transport system was discovered in rat cortex cuts, which system provides for the uptake of neurotransmitters released into the synaptic gap and, thus, for the termination of the neurotransmitter signal. The isolation of such a GABA transport protein was first accomplished in 1978.

According to more recent studies, with a proportion of 0.1 % of the membrane proteins, GABA uptake proteins occur relatively frequently in the nervous system. In the meantime four different representatives of neurotransmitter transport proteins could be detected by cloning and heterologous expression. The first representative of that family, the cloning whereof was accomplished starting from cDNA, was named GAT-1. This protein also is the first neurotransmitter transporter that was successfully cloned and expressed. Only shortly thereafter human GAT-1 was cloned.

1992 two further transport proteins were identified and named GAT-2 and GAT-3, respectively. Of these, the GAT-3 protein could also be cloned and expressed. GAT-2 probably plays only a minor role in the brains of mammals. It can only be found in the pia mater, as well as in the liver.

The forth representative of the family of uptake proteins is a common transport system for betaine and GABA which occurs, inter alia, in the kidney, and was named BGT-1.

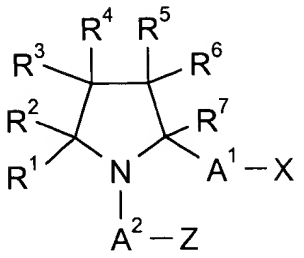
Already in 1975, in studies with nipecotic acid, guvacine and arecaidine, active agents from the betel nut (Arecha catechu), the inhibiting effect of nipecotic acid and guvacine on the uptake of GABA was discovered. With the knowledge about the relationships in the GABAergenic neurotransmission, new strategies in the therapy of epilepsy arose. For example, it is thus possible to enhance the neuronal GABA transmission by direct GABA mimetics. GABA itself is not suitable for this since it cannot pass the blood-brain barrier. A problem of said direct GABA mimetics is that a tolerance may develop thereby. Moreover, they amplify the GABAergenic neurotransmission in an unspecific manner in the GABAergenic synapses in general, and not only where signals arrive. Those mechanisms of action which enhance the GABAergenic neurotransmission only when transmitter is released represent a particularly sensible therapy approach. This can be achieved, one the one hand, by inhibiting the degradation of the transmitter and, on the other hand, by inhibiting the uptake thereof. The starting point for the development of corresponding GABA uptake inhibitors were the already mentioned compounds nipecotic acid and guvacine.

However, like GABA these compounds can pass the blood-brain barrier only with great difficulty or not at all.

Meanwhile some compounds which can pass into the CNS and at the same time show a substantial affinity towards GABA uptake proteins have been described in the literature. However, so far all of these compounds only show a high GAT-1 selectivity, whereas even today there are substantially no compounds which show GAT-3 selectivity.

Thus the problem underlying the present invention in general was the provision of new GABA uptake inhibitors and, in particular, the provision of GABA uptake inhibitors having a high selectivity towards GAT-3 (or at least high selectivity towards GAT-1).

According to the present invention the above problem is solved by compounds of the general formula (I)



(I)

wherein

R^1 to R^7 are independently selected from H, optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl, optionally substituted aryl or heteroaryl, OH, halogen (particularly F and Cl), CN, OR^{12}, SR^{12}, COR^{12}, $COOR^{12}$, SOR^{12}, SO_2R^{12}, $NR^{13}R^{14}$, $CONR^{13}R^{14}$, $SO_2NR^{13}R^{14}$, where R^{13} and R^{14} are independently selected from H and C_{1-3} alkyl and R^{12} represents C_{1-6} alkyl; two of R^1 to R^7 each may be combined to form a 3- to 6-membered ring system, which ring system may contain one or more heteroatoms; R^1 and R^2 and/or R^3 and R^4 and/or R^5 and R^6 may be replaced by an optionally substituted alkylidene group or =O; and two of R^1 to R^7 which are positioned at adjacent carbon atoms each may be replaced by a C-C bond;

A^1 represents $(-CR^8R^9-)_n$, optionally substituted C_{3-6} cycloalkylene or a combination of these groups, R^8 and R^9 being independently selected from H, C_{1-6} alkyl, halogen, OH, OR^{12} and $NR^{13}R^{14}$ and where for $n \geq 2$ R^8 and R^9 may be different in each group and two groups selected from R^8 and R^9 at adjacent C atoms may be replaced by a C-C bond, and a group -O- or -CO- may be positioned between two adjacent groups CR^8R^9; and wherein one of R^8 and R^9 may be combined with one of R^1 to R^7 to form a 5- to 7-membered ring structure; and n = 0, 1, 2, 3 or 4;

X is COOM or a group which can be converted into COOM under physiological conditions, M representing H or a pharmaceutically acceptable cation;

A^2 is $(-CR^{10}R^{11}-)_m$, where R^{10} and R^{11} are independently selected from H, C_{1-2} alkyl and halogen; where for $m \geq 2$ the groups R^{10} and R^{11} may be different in each group, a group

-O- or -S- may be positioned between two adjacent groups, and two groups selected from R^{10} and R^{11} at adjacent C atoms may be replaced by a C-C bond; and wherein one of R^{10} and R^{11} may be combined with one of R^1 to R^9 to form a 5- to 7-membered ring structure; and m is 1, 2, 3, or 4;

Z is selected from Y_3CO, $Y_2C=CR^{15}$ and $Y_2C=N-O$, where R^{15} is H, C_{1-3} alkyl or halogen and the groups Y independently are optionally substituted C_{6-12} aryl or optionally substituted C_{2-5} heteroaryl having up to three heteroatoms selected from N, O and S, and the groups Y may be linked by a covalent bond or by groups between atoms belonging to different groups Y, said groups selected from -O-, -S-, -NH-, -O-, -CH=CH-, -CH=N-, -CH_2- and -CH_2CH_2-;

as well as the individual stereoisomers of these compounds.

A further object of the present invention are pharmaceutical compositions containing at least one pharmaceutically acceptable carrier or excipient and at least one compound of general formula (I).

Furthermore, the present invention is directed to the use of the compounds of general formula (I) for the manufacture of a medicament for the treatment of diseases where amplification of the GABAergenic neurotransmission is of advantage, in particular epilepsy, Chorea Huntington and related disorders of the CNS. The compounds of the present invention can also successfully be employed as anticonvulsants, sedatives, anxiolytics and antidepressants.

In the following the present invention will be further illustrated with reference to preferred embodiments thereof.

Meanings of the radicals R^1 to R^7:

The term " optionally substituted C_{1-6} alkyl, C_{2-6} alkenyl and C_{2-6} alkynyl" is to denote groups that are unsubstituted or carry (preferably, one or two) substituents selected, in particular, from OH, halogen (particularly F, Cl, Br, and particularly preferred F), CN, NO_2 and OR^{12}. However, the substituents may also (and additionally) be (optionally substituted) aryl or heteroaryl radicals (as defined in more detail hereafter). As specific examples of the radicals R^1 to R^7 just discussed there may be mentioned methyl, ethyl, propyl, CF_3, CH_2OCH_3, CH_2OH, benzyl and phenethyl.

"Optionally substituted aryl or heteroaryl" includes aryl groups having preferably 6 to 12 C atoms and heteroaryl radicals having 5 to 12 ring members, up to three of which may be heteroatoms (in general selected from N, O and S). These aryl or heteroaryl radicals may be unsubstituted or substituted (by preferably one to three substituents). Preferred examples of such substituents are C_{1-3} alkyl, C_{2-4} alkenyl, OH, halogen (in particular, F, Cl, Br), CN, NO_2, OR^{12} and $NR^{13}R^{14}$. As specific examples there may be mentioned in this context phenyl, thienyl, furanyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, pyridinyl, pyranyl and corresponding radicals carrying one to three (preferably one) substituent from the group methyl, ethyl, CF_3, methoxy, ethoxy, F, Cl, CN, NH_2, dimethylamino and diethylamino.

If R^1 to R^7 represent halogen, said halogen preferably is fluorine or chlorine, particularly preferred fluorine. It is preferred for R^1, R^2 and R^7 to be different from halogen, OR^{12}, SR^{12} and $NR^{13}R^{14}$, since otherwise there is the possibility of enamine formation.

The radical R^{12} preferably is C_{1-3} alkyl, in particular methyl and ethyl. R^{13} and R^{14} are preferably the same and preferably represent methyl and ethyl. However, R^{13} and R^{14} may also form an alkylene group, resulting in, for example, a pyrrolidinyl or piperidinyl radical.

In a particularly preferred compound of general formula (I), R^1 to R^6 are independently selected from H, optionally substituted C_{1-3} alkyl, halogen, OH, CN, optionally substituted phenyl and optionally substituted heteroaryl having five to ten ring members

and one or two heteroatoms selected from O, N and S, and particularly from hydrogen, C_{1-3} alkyl and phenyl. R^7 preferably is H. In general it is preferred that not more than two and particularly not more than one of the radicals R^1 to R^7 is different from H. It may be of particular advantage if all of R^1 to R^7 represent hydrogen.

Also, two each of R^1 to R^7 may be combined to form a 3- to 6-membered ring system (preferably, a 5- or 6-membered ring system) which furthermore may contain one or more (preferably, one or two) heteroatoms. Preferably, the heteroatoms are O, N or S. Moreover, R^1 and R^2 and/or R^3 and R^4 and/or R^5 and R^6 may be replaced by an optionally substituted alkylidene group or oxo (=O). It is preferred that, if present at all, only one such alkylidene or oxo group is present on the ring. The substituents which may optionally be present on the alkylidene group (preferably one to three) are preferably those that have been given above as examples of substituents on alkyl, alkenyl and alkynyl radicals R^1 to R^7. Finally, two of R^1 to R^7, which are located on adjacent C atoms, each may be replaced by a C-C bond. This results in the presence of double and triple bonds in the ring. Preferred in this context is a double bond between the 3- and 4-position of the pyrrolidine skeleton. A pyrrole structure is also worth mentioning in this context.

If A^1 represents a combination of $(-CR^8R^9-)_n$ and (optionally substituted) C_{3-6} cycloalkylene, this is to mean that A^1 may, in particular, be alkylene-cycloalkylene, cycloalkylene-alkylene and alkylene-cycloalkylene-alkylene. It is preferred for A^1 to represent $(-CR^8R^9-)_n$. Regarding possible meanings of R^8 and R^9 the corresponding explanations in connection with R^1 to R^7 above may be referred to. Particularly preferred meanings of R^8 and R^9 are H and C_{1-3} alkyl, in particular methyl. Preferably, only one of R^8 and R^9 is different from H, and it is particularly preferred if both of them are hydrogen. n has values of, in particular, 0, 1 or 2, 1 or 2 being preferred. In the latter case the compounds of the present invention are derivatives of acetic and propionic acid (for R^8, R^9 = H). These compounds are particularly preferred according to the present invention.

If A^1 is, or includes, optionally substituted C_{3-6} cycloalkylene, preferred examples of the cycloalkylene group are cyclopropylene, cyclopentylene and cyclohexylene. Optionally present substituents are preferably selected from C_{1-3} alkyl, halogen (e.g., F or Cl) and OH. However, it is preferred for the cycloalkylene radical to not carry any substituents.

If A^1 is, or comprises, $(-CR^8R^9-)_n$, for $n \geq 2$ R^8 and R^9 may be different, both from each other and in each group CR^8R^9. Further, in this case two groups selected from R^8 and R^9 on adjacent C atoms each may be replaced by a C-C bond (which may result in a derivative of acrylic acid), and there may be a group -O- or -CO- between adjacent groups CR^8R^9, although this is not preferred. Finally, one of R^8 and R^9 (preferably located on a carbon atom which is bonded directly to the ring) may be combined with one of R^1 to R^7 (preferably, R^5, R^6 or R^7) to form a 5- to 7-membered ring structure. This ring structure may be saturated or unsaturated, and may also contain one or more heteroatoms, preferably selected from O, N and S.

In the general formula (I), X represents COOM or a group that can be converted into COOM under physiological conditions. Among the latter groups there are, for example, ester, nitrile and salts. Preferably, M represents hydrogen and corresponding cations of sodium, potassium, calcium and magnesium, as well as ammonium. H and Na are even more preferred as meanings of M, the most preferred meaning of M being hydrogen.

A^2 in the above general formula (I) is $(-CR^{10}R^{11}-)_m$, with R^{10} and R^{11} being preferably H, methyl, ethyl and halogen (in particular, F or Cl). Preferably only one of R^{10} and R^{11} is different from H, and it is particularly preferred for R^{10} and R^{11} to both represent hydrogen. If R^{10} and/or R^{11} are halogen, the halogen should not be on the C atom which is adjacent to the N atom (risk of formation of enamine or iminium ion). m preferably has a value of 2 or 3, 2 being particularly preferred. If $m \geq 2$ the groups R^{10} and R^{11} may be different, both from each other and within each group $CR^{10}R^{11}$. In particular for $m > 2$, two adjacent groups $CR^{10}R^{11}$ may be separated by a group -O- or -S-, and two groups selected from R^{10} and R^{11} on adjacent C atoms each may be replaced by a C-C bond, resulting in a double (or triple) bond. Also in these cases the C atom adjacent to the N

atom should be free of structural features which (may) result in an enamine or iminium ion structure, respectively. Finally, one of R^{10} and R^{11} (preferably located at the C atom bonded to the N atom) may be combined with one of R^1 to R^9 (preferably, with one of R^1, R^2, R^7, R^8 and R^9) to form a 5- to 7-membered ring structure, which ring structure may be saturated or unsaturated, and may further have one or more heteroatoms, selected from O, N and S, in addition to the ring nitrogen atom.

If Z stands for Y_3CO, the groups Y are preferably the same. Furthermore, preferred meanings of Y are optionally substituted phenyl as well as optionally substituted thienyl, furanyl and pyrrolyl. Optionally substituted phenyl is particularly preferred. If substituents are present, their number preferably does not exceed 3, and in particular 2, (only) one substituent being even more preferred. Preferred substituents are selected from C_{1-3} alkoxy, C_{1-3} alkyl, halogen, OH, NO_2, CN and $NR^{13}R^{14}$. Specific examples of such substituents are methoxy, ethoxy, methyl, ethyl, F, Cl, NH_2, dimethylamino and diethylamino. A particularly preferred substituent is C_{1-3} alkoxy, in particular methoxy. In the case of a phenyl ring this group is preferably in the 2- and/or 4-position, even more preferred in the 4-position.

If Z represents $Y_2C=CR^{15}$, the two groups Y are preferably the same as well. Furthermore, preferred meanings for Y in this case are optionally substituted phenyl or optionally substituted heteroaryl having 5 or 6 ring members and one or two hetereoatoms selected from O, N and S. Regarding the optionally present substituents, the above comments with respect to the groups Y may be referred to. If Y is phenyl, the phenyl ring is preferably free of substituents. If Y represents heteroaryl, Y preferably is optionally substituted thienyl, particularly 3-methyl-2-thienyl.

R^{15} preferably is H or methyl, even more preferred H.

If Z is $Y_2C=N-O$, the two groups Y preferably are also identical. With respect to the preferred meanings of Y the above comments regarding the preferred groups Y for the other meanings of Z may be referred to.

In particularly preferred embodiments of compounds of general formula (I) according to the present invention the various groups have the following meanings, in particular:

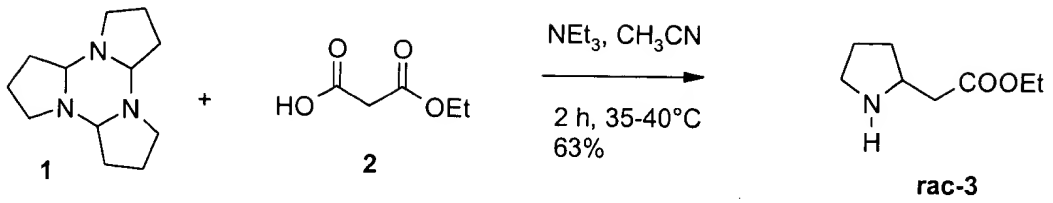
R^1 to R^7: hydrogen;
A^1: $-CH_2-$ or $-CH_2CH_2-$, as well as -CH=CH-;
X: COOH;
A^2: $-CH_2CH_2-$;
Z: $(C_6H_5)_2C=CH-$, (3-methyl-2-thienyl)$_2$C=CH- and $(4\text{-}CH_3O\text{-}C_6H_4)_3CO-$.

The present invention also includes the individual isomers (enantiomers, diastereomers, optionally cis/trans-isomers) of the compounds of general formula (I) of the present invention. In this context it is to be pointed out that irrespective of the meanings of the various radicals in the general formula, the carbon atom carrying R^7 and A^1-X is a chiral center, so that the compounds of the present invention are present as at least enantiomers. The present invention encompasses both the individual enantiomers and the racemates of these compounds.

The compounds of the present invention show a high selectivity towards GAT-3 and/or GAT-1 which is noteworthy; accordingly, they can be used for the treatment of conditions wherein these transport proteins play a role. Epilepsy and Chorea Huntington may particularly be mentioned in this context.

The compounds according to the present invention and the precursors thereof can be synthesized according to conventional processes described in the literature, or in analogy to such processes. In the following some of these processes will be briefly discussed. Individual isomers (enantiomers) may be prepared, in addition to a usual separation (e.g., by resolution of a racemate), also by processes which use chiral auxiliaries in the preparation. Examples of such processes will also be briefly outlined in the following.

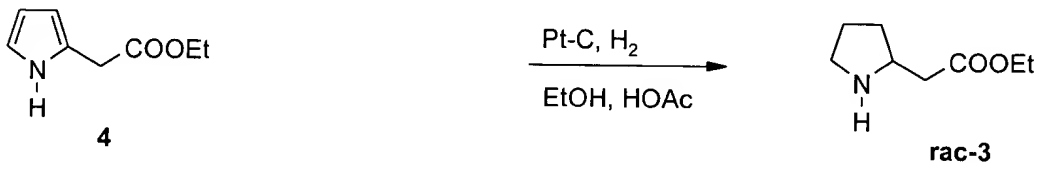
Reaction Scheme 1



1 2 rac-3

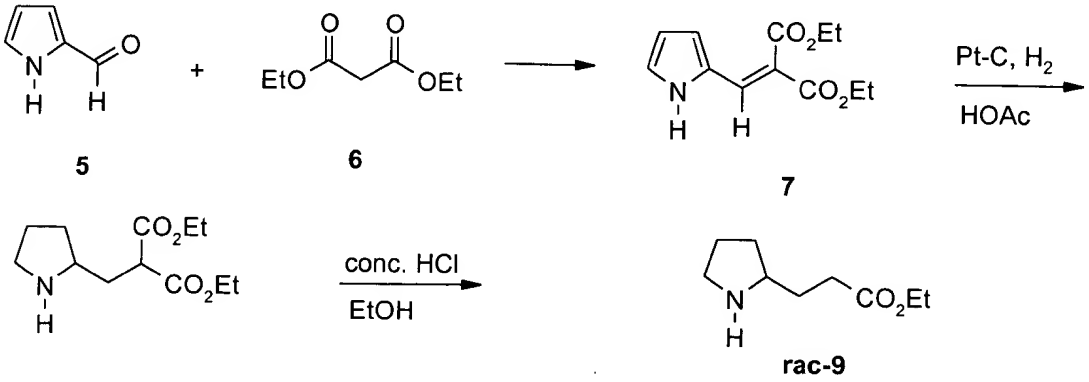
The synthesis of **rac-3** is carried out by reacting **1** with malonic acid monoethyl ester (**2**) according to the procedure of Fukawa et al., *Chem. Letters*, **1982**, 231-232.

Compound **rac-3** is furthermore available by catalytic hydrogenation of **4** with Pt-C as catalyst according to the following procedure: Clemo, Melrose, *J. Chem. Soc.*, **1942**, 424.



4 rac-3

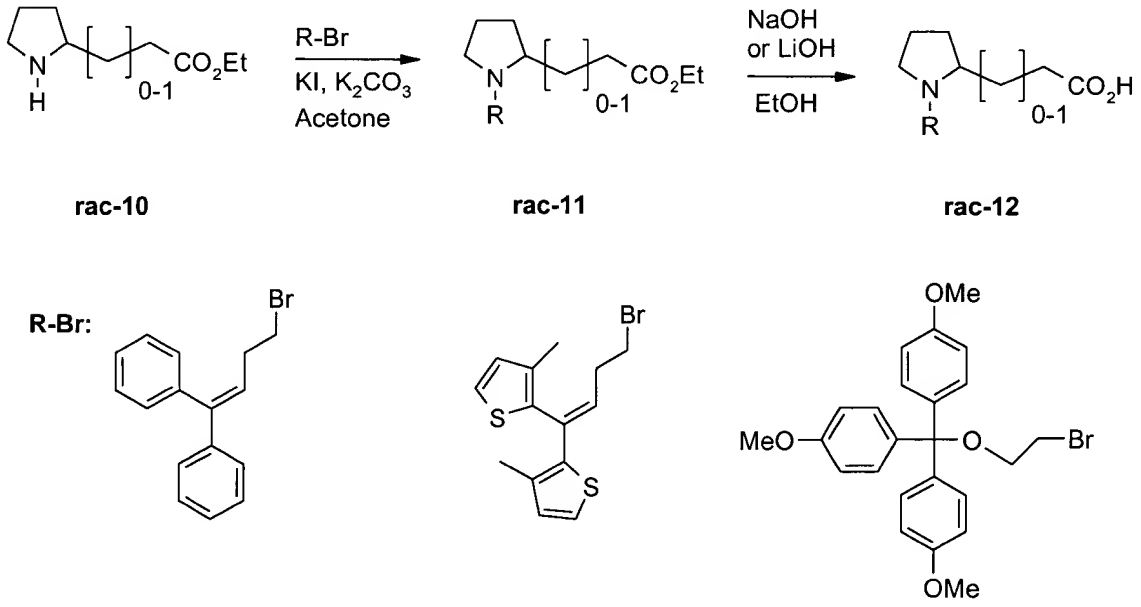
Reaction Scheme 2



5 6 7 rac-9

Compound **rac-9** may be synthesized starting from pyrrole-2-carbaldehyde **5** according to the three-step process depicted in Reaction Scheme 2. Condensation product **7** ist obtained by reacting **5** with **6** according to the procedure of Ch. Robinson, L. J. Wiseman, J. Leonhard, C. D. Slater, *Tetrahedron*, **1989**, 45, 4103-4112. Subsequent catalytic hydrogenation, ester hydrolysis and decarboxylation according to the procedure of Clemo et al., *J. Chem. Soc.*, **1950**, 1140 results in **rac-9**.

Reaction Scheme 3



In analogy to known processes, the N-substituted amino acids **rac-12** may be syntheized starting from the aminoacids **rac-10** by alkylation with a suitable electrophile and subsequent ester hydrolysis. K. E. Andersen et al., *J. Med. Chem.* **1993**, 36, 1716-1725. T. G. M. Dhar et al., *J. Med. Chem.* **1994**, 37, 2334-2342.

Preparation of Compounds in Enantiomericallly Pure Form

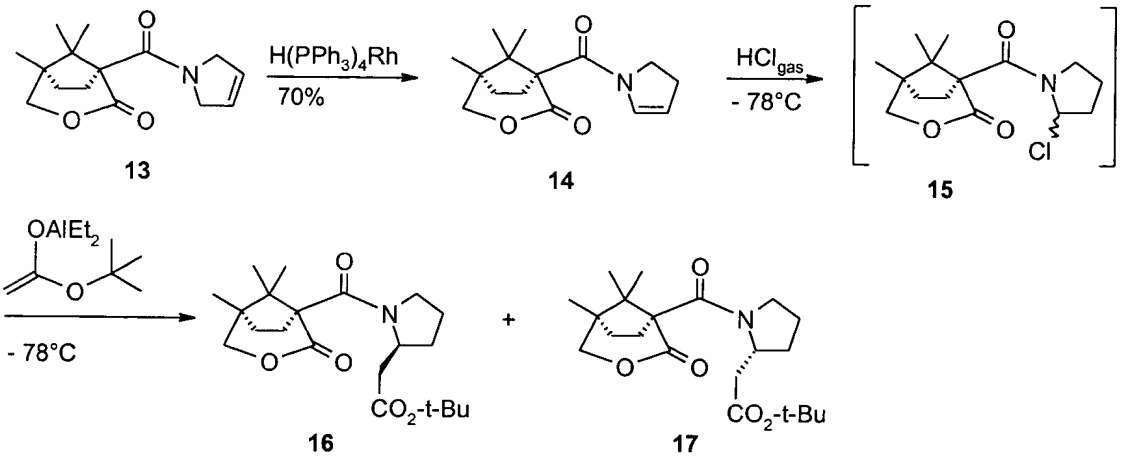
A) For the preparation of the compounds in enantiomerically pure form, for example, the racemates of the amino acid esters **rac-11** may be separated into their enantiomers according to known methods by using enantiomerically pure chiral acids. Hydrolysis of

the enantiomerically pure esters **11** thus obtained according to the already described methods results in the enantiomerically pure amino acids **12**.

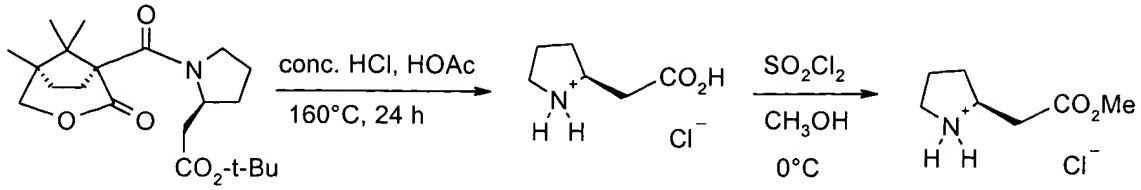
B) Compounds according to the present invention may, additionally, be prepared in enantiomerically pure form according to special processes. The reactions of the following Reaction Schemes **4** to **8** will be explained in the working examples below.

Basic Skeleton of Pyrrolidine-2-acetic acid

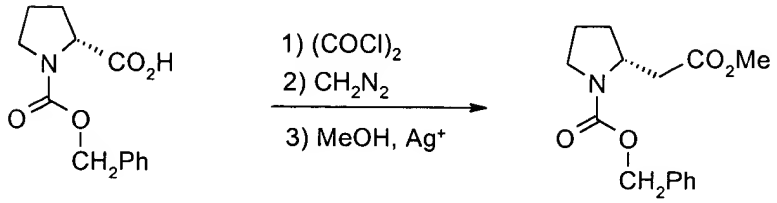
Reaction Scheme 4



Reaction Scheme 5



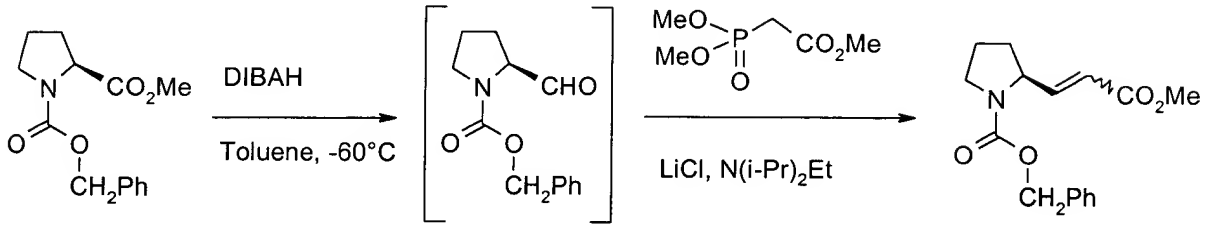
16 **S-18-HCl** **S-19-HCl**



R-20 **R-21**

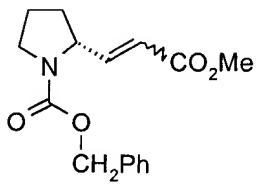
Basic Skeleton of Pyrrolidin-2-ylpropanoic Acid

Reaction Scheme 6



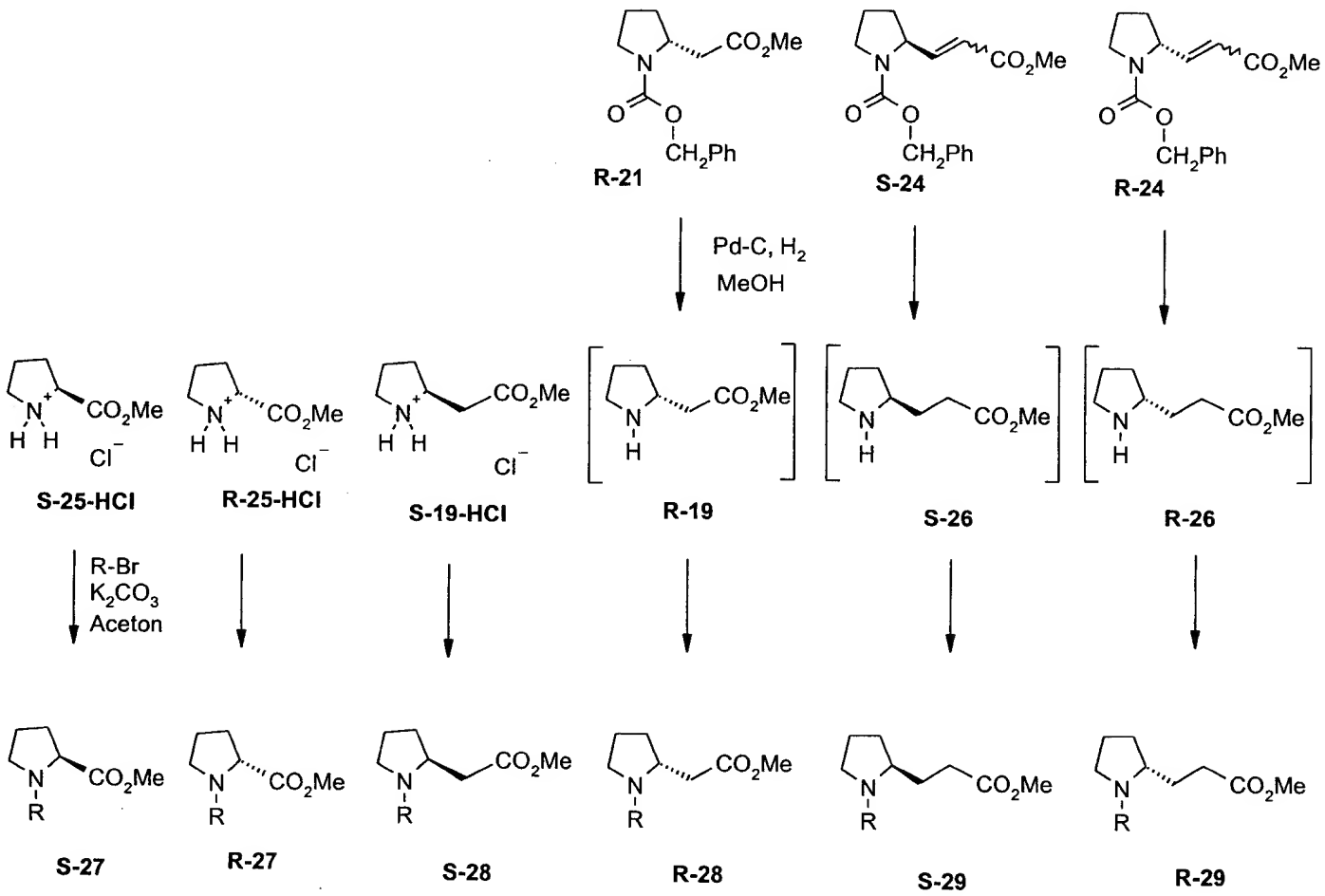
S-22 **S-23** **S-24**

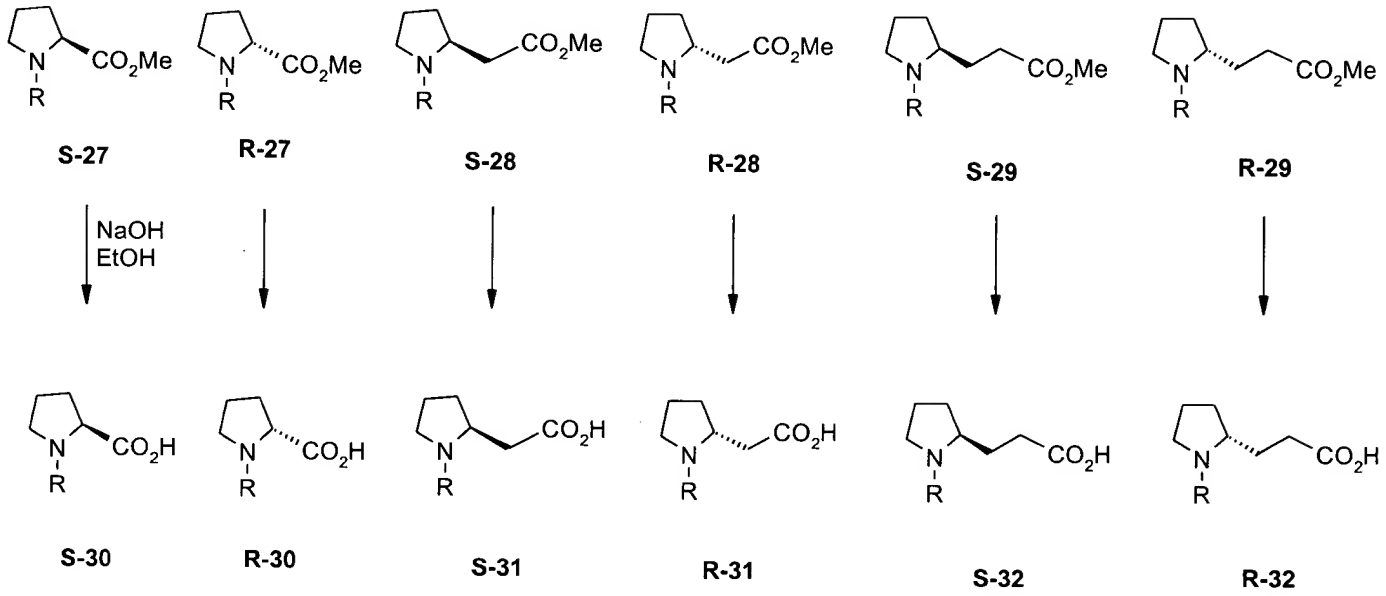
Preparation by mirror-like reaction sequence in analogy to above



R-24

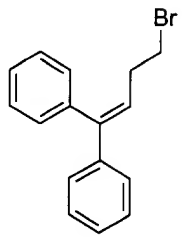
Reaction Scheme 7



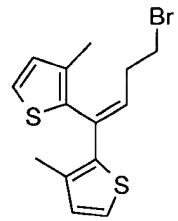

S-27
R-27
S-28
R-28
S-29
R-29
NaOH
EtOH
S-30
R-30
S-31
R-31
S-32
R-32

R-Br:

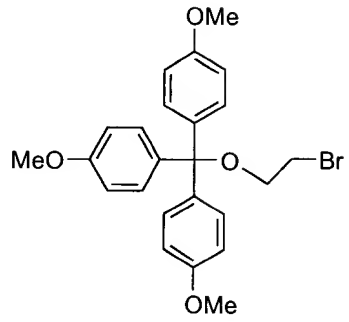
a


Br

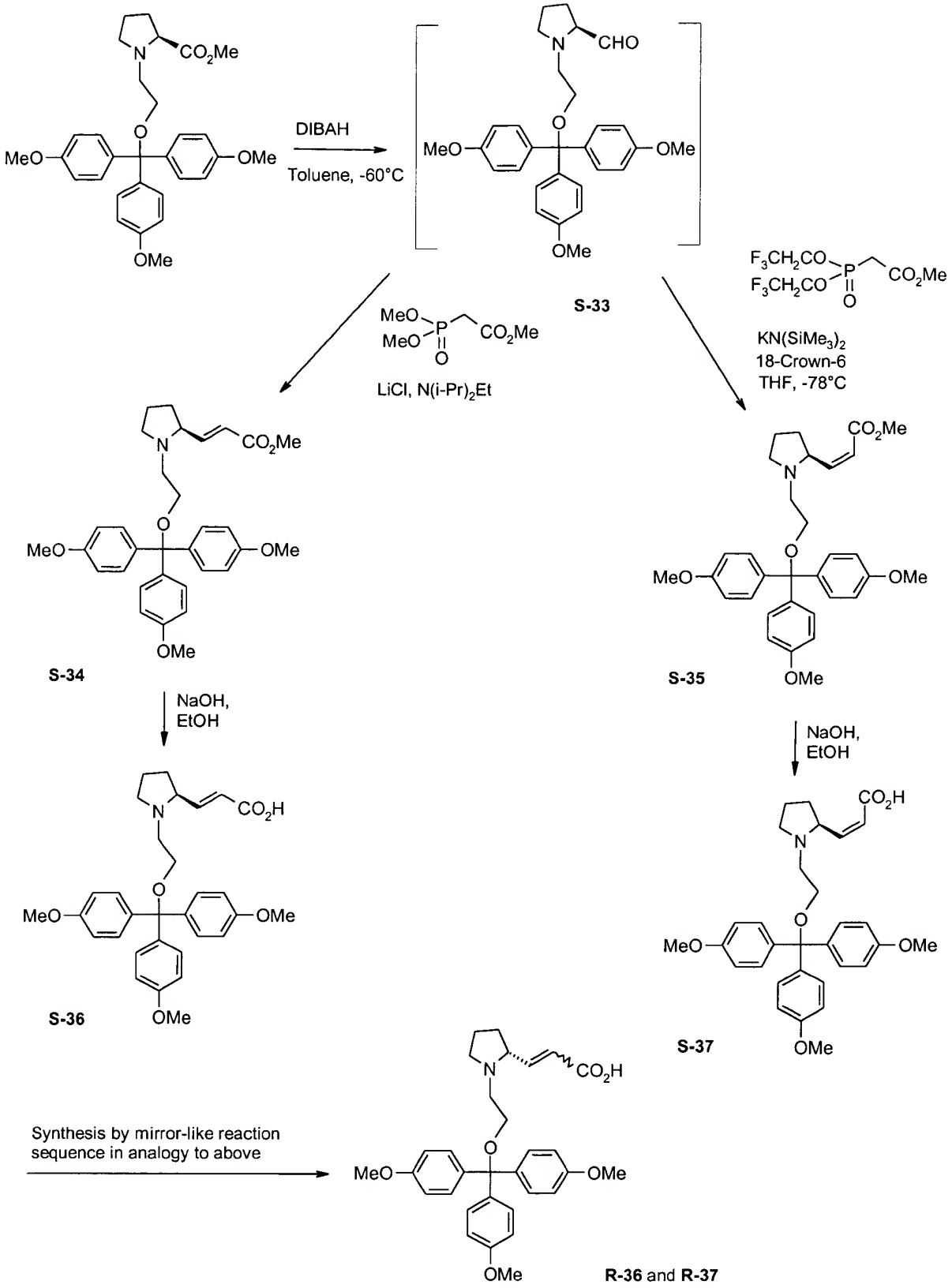
b


Br
S
S

c


OMe
MeO
O
Br
OMe

Reaction Scheme 8



Examples

General details of chemical studies

Melting Points: Melting point apparatus according to Dr. Tottoli (Messrs.Büchi, No. 512). The melting points were not corrected.

Optical Rotations: Polarimeter 241 MC (Messrs. Perkin Elmer).

IR Spectra: FT-IR Spectrometer 1600 and Paragon 1000 (Messrs. Perkin Elmer). The spectra were recorded with a KBr pellet or as film between NaCl plates, respectively.

NMR Spectra: JNMR-GX 400 (Messrs. Jeol, 400 MHz), TMS as internal standard. Coupling constants were given with an accuracy of 0.5 Hz. The post-processing of the spectra was conducted with NUTS, 2D version 4.35, Acorn NMR, 1994.

Mass Spectra: Mass Spectrometer 5989 A with 59980 B Particle Beam LC/MS Interface (Messrs. Hewlett Packard).

Thin Layer Chromatography: DC plates Kieselgel 60 F-254 (Messrs. Merck). Detection was carried out in the UV range (254 nm) or by using a cerium(IV) ammonium molybdate immersion reagent (5 % $(NH_4)_xMo_7O_{24}$ and 0.2 % $Ce(SO_4)_2$, dissolved in 5 % aqueous H_2SO_4). Detection was carried out by subsequent heating.

Column Chromatography (CC): Flash-Chromatography [113] on Kieselgel 60 (particle size 0.040 - 0.063 mm, Messrs. Merck).

Analytical HPLC: Chromatography pumps L-6200 Intelligent-Pump and L-6000 (Messrs. Merck-Hitachi), UV-VIS Detectors L-4000 and L-7400 (242 and 254 nm, respectively, Messrs. Merck-Hitachi), integrators D-7500 and D-2500 (Messrs. Merck-Hitachi), columns: cartridge system LiChroCart® (Messrs. Merck):

A) LiChrospher® Si 60 (5 µm, 250 × 4 mm with precolumn 4 × 4 mm)

B) LiChrosorb® Si 60 (5 µm, 250 × 4 mm with precolumn 4 × 4 mm).

Preparative HPLC: Chromatography pump L-6000 (Messrs. Merck-Hitachi), UV-VIS detector L-4000 (242 and 254 nm, respectively, Messrs. Merck-Hitachi), integrator D-2000 (Messrs. Merck-Hitachi),

Column: Hibar Fertigsäule RT (Messrs. Merck) LiChrosorb® Si 60 (7 µm, 250 × 25 mm).

Reagents and solvents: All reagents were of commercial grade. Dried and distilled solvents were used for the reactions. For chromatography, distilled solvents were used which were additionally degassified for HPLC.

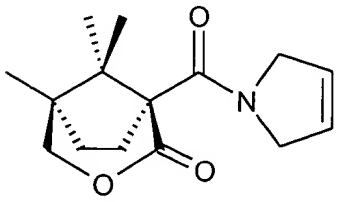
Reaction Conditions: If not indicated otherwise, the reactions were carried out in previously heated glass apparatus under N_2 atmosphere.

The following abbreviations were used in the description of the experiments:

DBU	1,8-Diazabicyclo[5.4.0.]un-7-decene
DIBAH	Diisobutyl aluminiumhydride
DIPEA	Diisopropyl ethylamine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
Ether	Diethyl ether
THF	Tetrahydrofuran
TMEDA	N,N,N′,N′-Tetramethylethylene diamine
i. vac.	in vacuo

Preparation Example 1

(1*S*,5*R*)-1-(2,5-Dihydropyrrol-1-ylcarbonyl)-5,8,8-trimethyl-3-oxabicyclo[3.2.1] octan-2-one (13)

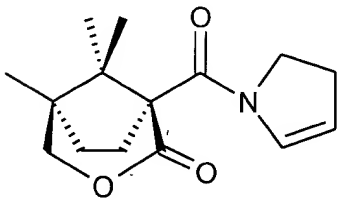


13

3.79 g (14.4 mmol) of (1*S*,5*R*)-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one-1-carboxylic acid was suspended in 60 ml of CH_2Cl_2, cooled to 0 °C, and 1.78 g (14.5 mmol) of oxalyl chloride was added thereto. Subsequently DMF (10 drops) was added under strong stirring and the reaction mixture was slowly heated to room temperature. After the evolution of gas had ceased, the flask was purged with a nitrogen stream for one hour to remove HCl. Upon cooling the solution to 0 °C, 3.54 g (2.5 eq.) of triethylamine as well as 1 g (14.4 mmol) of 3-pyrroline were added. Thereafter the reaction mixture was brought to room temperature and stirred for 12 h. Subsequently the reaction mixture was diluted with 30 ml of CH_2Cl_2, washed several times with 0.5 N HCl, and the organic phase was dried with $MgSO_4$ and concentrated. Purification of the residue by column chromatography (petrol ether/ethyl acetate = 7/3) and recrystallization from petrol ether/ethyl acetat (7/3) afforded 3.254 g (86%) of colorless crystals; m.p.: 108 °C. $[\alpha]_D^{20} = +97.9$ (c = 0.65, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 0 °C): δ = 0.91 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.86-1.97 (m, 2 H, CH_2CH_2), 2.27 (dt, J = 11.0/5.1 Hz, 1 H, CH_2CH_2), 2.43 (ddd, J = 13.9/11.0/5.9 Hz, 1 H, CH_2CH_2), 3.94 (d, J = 11.3 Hz, 1 H, CH_2O), 4.15 (dd, J = 11.3/2.2 Hz, 1 H, CH_2O), 4.12-4.18 (m, 1 H, NCH_2), 4.23 (ddd, J = 13.9/4.4/2.2 Hz, 1 H, NCH_2), 4.39 (ddd, J = 13.9/5.1/2.2 Hz, 1 H, NCH_2), 4.56 (ddd, J = 16.9/5.1/2.2 Hz, 1 H, NCH_2), 5.75 (ddd, J = 6.6/4.4/2.2 Hz, 1 H, HC=), 5.85 (ddd, J = 6.6/4.4/2.2 Hz, 1 H, HC=).

Preparation Example 2

(1*S*,5*R*)-1-(2,3-Dihydropyrrol-1-ylcarbonyl)-5,8,8-trimethyl-3-oxabicyclo[3.2.1] octan-2-one (14)



14

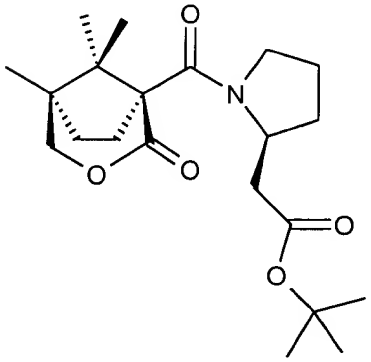
A mixture of 1.0 g of **13** (3.8 mmol) and 15 mg of hydridotetrakis(triphenylphosphine)-rhodium dissolved in 4 ml of abs. xylene was stirred for 44 h at 140 °C in a sealed pressure tube. Subsequently the reaction mixture was filtered, concentrated, purified by column chromatography (petrol ether/ethyl acetate /ethyldimethylamine = 80/20/1), and recrystallized from cyclohexane. Yield: 700 mg (70%); colorless crystals; m.p.: 105 °C. $[\alpha]_D^{20}$ = + 46.3 (c = 0.68, $CHCl_3$). – ^{1}H NMR ([D_5]nitrobenzene, 130 °C): δ = 0.91 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.80-2.00 (m, 2 H, CH_2CH_2), 2.18-2.33 (m, 1 H, CH_2CH_2), 2.45-2.70 (m, 3 H, NCH_2CH_2, CH_2CH_2), 3.89-3.96 (m, 2 H, NCH_2), 3.99 (d, *J* = 11.0 Hz, 1 H, CH_2O), 4.19 (dd, *J* = 11.0/2.2 Hz, 1 H, H_2O), 5.11-5.20 (m, 1 H, NCH=C*H*), 6.71-6.79 (m, 1 H, NCH=).

Preparation Example 3

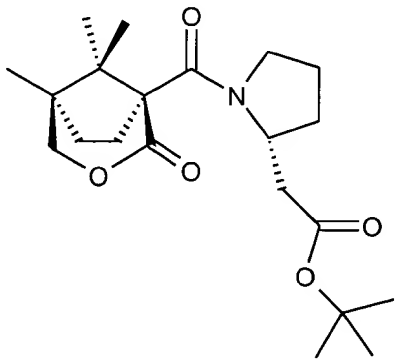
(a) Electrophilic α-Amidoalkylation, General Procedure

At –85 °C gaseous HCl was introduced into anhydrous CH_2Cl_2 (1 ml per 0.1 mmol of **14**) over a period of 20 min. Enamide **14**, dissolved in CH_2Cl_2 (0.5 ml per 0.1 mmol), was then slowly added dropwise under strong stirring. The introduction of gaseous HCl was not stopped and was continued for 10 - 20 min. Thereafter excess HCl gas was removed for 1 h at -78 °C in high vacuum. Then a solution of the respective organometallic reagent was added dropwise to the obtained reaction mixture. After the indicated reaction time hydrolysis (H_2O) was effected at -78 °. After the phases had separated the aqueous phase was extracted four times with CH_2Cl_2, and the organic phases were washed with saturated NaCl solution, dried with $MgSO_4$ and concentrated in vacuo. The isolated residue was treated further as indicated.

(b) Preparation of
(1,1-Dimethylethyl)-{(*2S*)-N-[(*1S,5R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]pyrrolidin-2-yl}acetate (16) and
(1,1-Dimethylethyl)-{(*2R*)-N-[(*1S,5R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]pyrrolidin-2-yl}acetate (17)



16



17

Preparation of the reagent:

1.5 ml (2.4 mmol) of *n*-butyllithium (1.6 M in hexane) was added dropwise to a solution of 315 µl (2.4 mmol) of diisopropylamine in 2.4 ml of anhydrous THF at -78 °C. After 30 min of stirring 320 µl (2.4 mmol) of *tert*-butyl acetate was added. Stirring was continued for 40 min, with heating up to -30 °C. Thereafter 2.4 ml (2.4 mmol) of diethyl aluminumchloride solution (1 M in hexane) was added and again stirred for 20 min. The entire amount of reagent was used.

Electrophilic α-amidoalkylation, general procedure: 0.158 g (0.6 mmol) of **14**, 6.6 ml (= 4 eq.) of organometallic reagent (see above), 16 h, -78 °C. CC (petrol ether/ethyl acetate = 7/3) afforded 203 mg (89.1 %) of **16** and **17** as mixture of diastereomers. HPLC analysis (column B; heptane/ethyl acetate = 80/20; 1.5 ml/min): **16**: t_{ret} = 16.1 min, 81.2%; **17**: t_{ret} = 20.4 min, 18.8%. Separation was effected by preparative HPLC (*n*-heptane / ethyl acetate = 82/18; 13.5 ml/min; **16**: t_{ret} = 33.8 min; **17**: t_{ret} = 43.6 min).

16: Yield: 154 mg (67.6 %); colorless crystals, m.p.: 135 °C. – $[\alpha]_D^{20}$ = + 18.2 (c = 1.07, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 0.88 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.43 (s, 9 H, $C(CH_3)_3$), 1.63-1.69 (m, 1 H, $NCH_2CH_2CH_2$), 1.74-1.96 (m, 4 H, $NCH_2CH_2CH_2$, CH_2CH_2), 2.14-2.24 (m, 2 H, CH_2CH_2), 2.31-2.43 (m, 2 H, CH_2CH_2, CH_2COO), 2.85 (dd, *J* = 15.5/3.8 Hz, 1 H, CH_2COO), 3.21 (td, *J* = 9.5/6.5 Hz, 1 H, NCH_2), 3.72 (ddd, *J* = 9.5/7.3/2.4 Hz, 1 H, NCH_2), 3.91 (d, *J* = 11.0 Hz, 1 H, $CH_2OC{=}O$), 4.12 (dd, *J* = 11.0/2.2 Hz, 1 H $CH_2OC{=}O$), 4.42 (qd, *J* = 8.1/3.8 Hz, 1 H, NCHC).

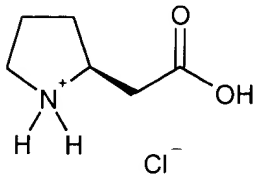
17: Yield: 36 mg (15.8 %); colorless crystals, m.p.: 89 °C.

$[\alpha]_D^{20}$ = + 56.6 (c = 1.1, $CHCl_3$). – ^{1}H NMR ([D_5]nitrobenzene, 140 °C): δ = 0.88 (s, 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 1.51 (s, 9 H, $C(CH_3)_3$), 1.82-2.06 (m, 6 H, $NCH_2CH_2CH_2$, CH_2CH_2), 2.26 (ddd, *J* = 15.0/10.0/5.6 Hz, 1 H, CH_2CH_2), 2.35 (dd, *J* = 15.6/9.3 Hz, 1 H, CH_2COO), 2.61-2.72 (m, 1 H, CH_2CH_2), 3.18 (dd, *J* = 15.6/3.7 Hz, 1 H, CH_2COO), 3.43-3.50 (m, 1 H, NCH_2), 3.62 (dt, *J* = 10.6/6.9 Hz, 1 H, NCH_2), 3.92 (d,

J = 11.1 Hz, 1 H, $CH_2OC{=}O$), 4.17 (dd, J = 11.1/2.0 Hz, 1 H, $CH_2OC{=}O$), 4.60-4.67 (m, 1 H, NCHC).

Preparation Example 4

(*S*)-2-Pyrrolidinoacetic acid (S-18-HCl)



S-18-HCl

325 mg (0.87 mmol) of **16** were dissolved in 4 ml of conc. acetic acid, 6 ml of conc. HCl were added thereto, and heating in a pressure tube was conducted for 24 h at 160 °C. Subsequently the reaction mixture was cautiously poured onto 15 ml of ice water and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and concentrated i. vac.. The yield of auxiliary was 131 mg (71 %). The aqueous phase was concentrated i. vac. and brought to dryness in high vacuum. The yield of pyrrolidinoacetic acid hydrochloride was 102 mg (70.8 %). For the determination of rotation and melting point a recrystallization from acetone/ methanol/Et_2O was carried out. Colorless crystals, m.p.: 173-175 °C, $[\alpha]_D^{23}$ =+ 19.1 (c = 1.2, H_2O) Lit.: [T. Govindachari, T. Rajagopalan, N. Viswanathan, *J. Chem. Soc. Perkin Trans. 1* , **1974**, 1161-1165.] 175-176 °C, $[\alpha]_D^{28}$ = + 19.3 (c = 1.74, H_2O). – ^{1}H NMR (CD_3OD, 20 °C): δ = 1.66-1.79 (m, 1 H, $NCH_2CH_2CH_2$), 1.92-2.16 (m, 2 H, $NCH_2CH_2CH_2$), 2.21-2.32 (m, 1 H, $NCH_2CH_2CH_2$), 2.74-2.92 (m, 2 H, CH_2COO), 3.26-3.34 (m, 2 H, NCH_2), 3.79-3.89 (m, 1 H, NCHC).

Preparation Example 5

(*S*)-Pyrrolidin-2-yl-acetic acid methyl ester hydrochloride (S-19-HCl)

At 0 °C, 0.3 ml (4.2 mmol) of thionyl chloride was added dropwise to 1.2 ml of methanol. Thereafter 173 mg (1.05 mmol) of (S)-homoproline hydrochloride (**S-18-HCl,** see Preparation Example 4) was added. The reaction mixture was slowly heated to room temperature and stirred for 24 h at room temperature. Thereafter concentration in an aspirator vacuum and drying of the residue in high vacuum were conducted. Yield 176 mg (93.8 %) of colorless crystals. M.p.: 53 °C. $[\alpha]_D^{20} = +3.3$ (c = 1.2, $CHCl_3$) lit.: [T. Govindachari, T. Rajagopalan, N. Viswanathan, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1161.] $[\alpha]_D^{20} = +3.4$ (c = 2.0, $CHCl_3$)]. – MS (70 eV); *m/z* (%): 143 (33) [M^+], 128 (29), 115 (53), 110 (100).

Preparation Example 6

(*R*)-1-Benzyloxycarbonylpyrrolidin-2-yl-acetic acid methyl ester (R-21)

The synthesis was conducted according to lit. (J.-M. Casal, A. Fürst, W. Meier, *Helv. Chim. Acta* **1976**, *59*,1917-1924.), starting from 249 mg (1 mmol) of (*R*)-1-benzyloxy-carbonylproline (**R-20**) via (*R*)-2-diazoacetylpyrrolidine-1-carboxylic acid benzyl ester. Yield: 113 mg (40.8%); colorless oil.

Preparation Example 7

(*S*)-N-Benzyloxycarbonylproline methyl ester (S-22)

The synthesis was conducted according to lit.: R. Nurdinov, E. Liepin`sh, I. Kalvin`sh, *Chem. Heterocycl. Compd.* **1993**, *29*, 1352- 1357. Batch size: 15 mmol (2.48 g); yield: 3.79 g (96%); colorless oil.

Preparation Example 8

(*R*)-N-Benzyloxycarbonylproline methyl ester (R-22)

The synthesis was conducted according to the procedure for **S-22**. Batch size: 9.17 mmol (1.52 g); yield: 2.31 g (96%); colorless oil.

Preparation Example 9

(2*E*)-3-[(2*S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester and (2*Z*)-3-[(2*S*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl] acrylic acid methyl ester (S-24)

The synthesis was conducted according to lit.. [R. Grote, A. Zeeck, J. Stümpfel, H. Zähner, *Liebigs Ann. Chem.* **1990**, *29*, 525-530; T. Sato, K.Tsujimoto, K. Matsubayashi, H. Ishibashi, M. Ikeda, *Chem. Pharm. Bull.* **1992**, *40*, 2308-2312.]
At -60 °C, 18 ml of DIBAH solution (1 M in hexane) was added dropwise to a solution of 2.346 g (8.92 mmol) of **S-22** in 50 ml toluene over 15 min , and the reaction mixture was stirred for 1 h at -60 °C. Subsequently the reaction was stopped by dropwise addition of 2 ml of methanol, heated to RT and taken up in 1 N HCl and Et_2O. The aqueous phase was extracted three times with Et_2O, and the combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. The oily residue (2.07 g) was dissolved in 35 ml of acetonitrile, and 454 mg (10.7 mmol, 1.2 equiv.) of LiCl and 1.86 ml (10.7 mmol, 1.2 equiv.) of DIPEA were added thereto. Thereafter 1.73 ml (10.7 mmol, 1.2 equiv.) of trimethyl-phosphonoacetate was added dropwise. The reaction mixture was stirred for 16 h at RT, then concentrated i. vac., taken up with Et_2O and water, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. CC (petrol ether/ethyl acetate = 7/3) afforded 1.88 g (72.9%) of a colorless oil.

Preparation Example 10

(2*E*)-3-[(2*R*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester and (2*Z*)-3-[(2*R*)-1-(Benzyloxycarbonyl)pyrrolidin-2-yl]acrylic acid methyl ester (R-24)

The synthesis was conducted according to the procedure for **S-24**. Batch size: 7.03 mmol (1.85 g); yield: 1.48 g (72.8%); colorless oil.

Preparation Example 11

(*S*)-Proline methyl ester hydrochloride (S-25-HCl)

The synthesis was conducted according to lit.: D. Hoogwater, M. Peereboom, *Tetrahedron* **1990**, *46*, 5325-5332; J. Pastuszak, J. Gardener, J. Singh und D. Rich, *J. Org. Chem.* **1982**, *47*, 2982-2987. Batch size: 43.5 mmol (5.02 g); yield: 6.8 g (94%); m.p.: 72 °C (lit.: 73 °C).

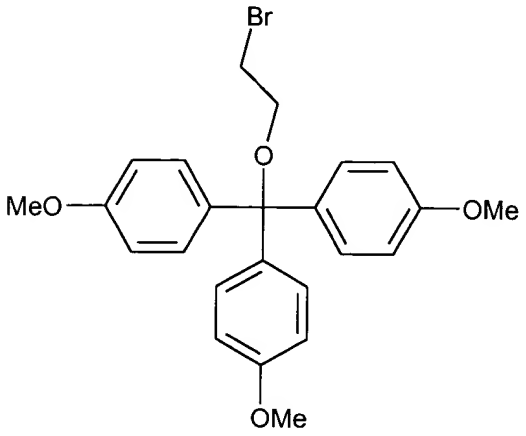
Preparation Example 12

(*R*)-Proline methyl ester hydrochloride (R-25-HCl)

The synthesis was conducted according to lit.: D. Hoogwater, M. Peereboom, *Tetrahedron* **1990**, *46*, 5325-5332; J. Pastuszak, J. Gardener, J. Singh und D. Rich, *J. Org. Chem.* **1982**, *47*, 2982-2987. Batch size: 43.5 mmol (5.02 g); yield: 7.0 g (97%); m.p.: 71 °C (lit. 73 °C).

Preparation Example 13

2-[(Trismethoxyphenyl)methoxy]ethyl bromide (R-Br c)



R-Br c

50 µl of conc. H_2SO_4 was added dropwise to a solution of 1.05 g (3 mmol) of tris-(4-methoxyphenyl)methanol in 5 ml of benzene, and the reaction mixture was heated to 65 °C for 5 min. Upon the addition of 318 µl (4.5 mmol) of bromoethanol the reaction mixture was stirred for additional 60 min at RT. Then it was taken up in Et_2O and water, the aqueous phase was extracted three times with Et_2O, dried ($MgSO_4$) and concentrated i. vac.. CC (petrol ether/Et_2O = 9/1) of the oily residue afforded 464 mg (33.8%) of a colorless oil. Additionally 564 mg (53.7%) of tris(4-methoxyphenyl)methanol could be recovered.

^1H NMR ($CDCl_3$, 20 °C): δ = 3.37-3.46 (m, 4 H, NCH_2CH_2O), 3.79 (s, 9 H, OCH_3), 6.81-6.86 (m, 6 H, aromat. H), 7.32-7.37 (m, 6 H, aromat. H).

Example 1

(a) N-Alkylation of the pyrrolidinylalkane carboxylic acid esters

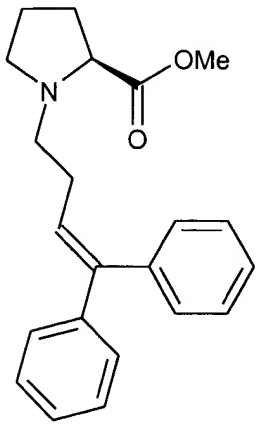
General Procedure A

To a suspension of the hydrochloride of the indicated pyrrolidinylalkanecarboxylic acid ester (1 equiv.), 0.1 equiv. of potassium iodide and 2 equiv. of potassium carbonate in acetone (1.5 ml/mmol), 1 equiv. of the indicated bromide, dissolved in acetone (1 ml/mmol) was added dropwise. The mixture was stirred at room temperature for the indicated time, taken up in water and CH_2Cl_2, extracted three times with CH_2Cl_2, dried ($MgSO_4$) and concentrated i. vac.. The isolated residue was treated further as indicated.

General Procedure B

To a solution of the indicated Cbz-protected amino acid alkyl ester (= 1 equiv.) in MeOH (0.1 M) was added a spatula tip full of Pd/C and the solution was stirred under H_2 atmosphere at normal pressure (balloon) for 1 h at RT. After the catalyst had been filtered off a concentration i. vac. was conducted, and the obtained residue was suspended in acetone (1.5 ml/mmol) with 1 equiv. of potassium carbonate and 0.1 equiv. of potassium iodide. Subsequently 1 equiv. of the indicated bromide, dissolved in acteone (1 ml/mmol), was added dropwise. The mixture was stirred at room temperature for the indicated time, taken up in water and CH_2Cl_2, extracted three times with CH_2Cl_2, dried ($MgSO_4$) and concentrated i. vac.. The isolated residue was treated further as indicated.

(b) (*S*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid methyl ester (S-27a)



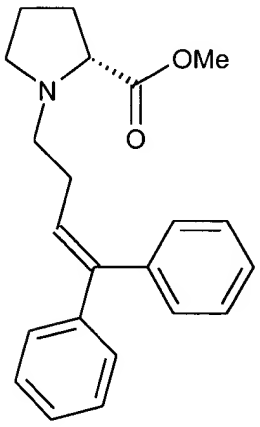
S-27a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 497 mg (3 mmol) of L-proline methyl ester hydrochloride (**S-25-HCl**, see Preparation Example 11), 49.8 mg (0.3 mmol) of potassium iodide, 829 mg (6 mmol) of potassium carbonate, 861 mg (3 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 527 mg (52.4 %) of a colorless oil.

$[\alpha]_D^{20}$ = –35.7 (c = 2.79, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.70-1.85 (m, 1 H, NCH_2CH_2), 1.85-1.96 (m, 2 H, $NCH_2CH_2CH_2$), 2.02-2.14 (m, 1 H, $NCHCCH_2$), 2.27-2.37 (m, 3 H, NCH_2, $=CCH_2CH_2N$), 2.49-2.57 (m, 1 H, $=CCH_2CH_2N$), 2.81 (dt, *J* = 11.5/8.1Hz, 1 H, $=CCH_2CH_2N$), 3.11 (td, *J* = 8.1/3.0 Hz, 1 H, NCH_2), 3.16 (dd, *J* = 8.7/5.9 Hz, 1 H, NCHCOO), 3.68 (s, 3 H, OCH_3), 6.08 (t, *J* = 7.4 Hz, 1 H, =CH), 7.15-7.40 (m, 10 H, aromat. H).

(c) (*R*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid methyl ester (R-27a)

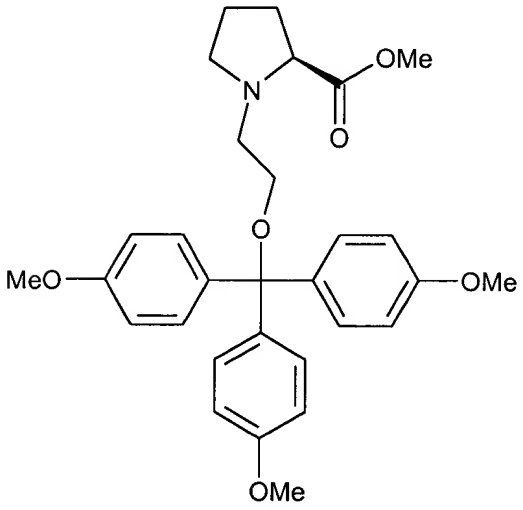


R-27a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 359 mg (2.17 mmol) of D-proline methyl ester hydrochloride (**R-25-HCl**, see Preparation Example 12), 36 mg (0.217 mmol) of potassium iodide, 600 mg (4.34 mmol) of potassium carbonate, 623 mg (2.17 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 48 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 350 mg (48.1 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-27a**. $[\alpha]_D^{20} = +34.9$ (c = 1.72, $CHCl_3$).

(d) (*S*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid methyl ester (S-27c)

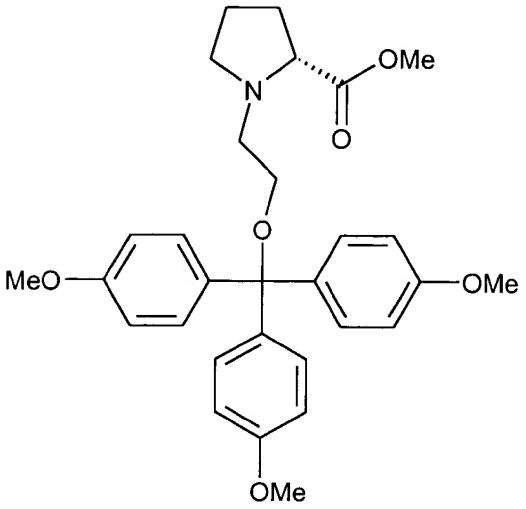


S-27c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 248 mg (1.5 mmol) of L-proline methyl ester hydrochloride (**S-25-HCl**, see Preparation Example 11), 24.9 mg (0.15 mmol) of potassium iodide, 415 mg (3 mmol) of potassium carbonate, 686 mg (1.5 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 40 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 285 mg (37.6 %) of a colorless oil. $[\alpha]_D^{20} = -29.6$ (c = 1.05, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.73-1.81 (m, 1 H, NCH_2CH_2), 1.81-1.93 (m, 2 H, $NCH_2CH_2CH_2$), 2.02-2.14 (m, 1 H, $NCHCCH_2$), 2.43 (q, *J* = 8.7 Hz, 1 H, NCH_2), 2.73 (dt, *J* = 12.6/6.3 Hz, 1 H, OCH_2CH_2N), 2.95 (dt, *J* = 12.6/6.3 Hz, 1 H, OCH_2CH_2N), 3.09-3.16 (m, 1 H, NCH_2), 3.21 (t, *J* = 6.3 Hz, 2 H, OCH_2CH_2N), 3.26 (dd, *J* = 8.9/5.8 Hz, 1 H, NCHCOO), 3.65 (s, 3 H, $COOCH_3$), 3.78 (s, 9 H, OCH_3), 6.79-6.83 (m, 6 H, aromat. H), 7.29-7.34 (m, 6 H, aromat. H).

(e) (*R*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid methyl ester (R-27c)

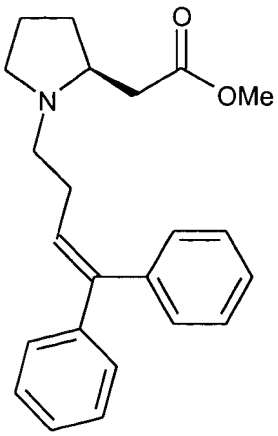


R-27c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 331 mg (2.0 mmol) of D-proline methyl ester hydrochloride (**R-25-HCl**, see Preparation Example 12), 33.2 mg (0.2 mmol) of potassium iodide, 553 mg (4.0 mmol) of potassium carbonate, 914 mg (2.0 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 40 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 395 mg (39.1 %) of a colorless oil. The analytical data (^{1}H NMR, IR, MS) of the compound is in agreement with that of the (*S*)-enantiomer **S-27c**. $[\alpha]_D^{20} = +30.5$ (c = 1.75, $CHCl_3$).

(f) (*S*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-yl]acetic acid methyl ester (S-28a)



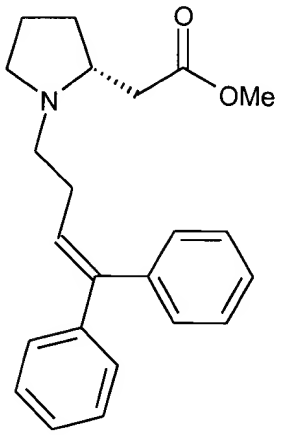
S-28a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 176 mg (0.983 mmol) of (*S*)-pyrrolidin-2-ylacetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 16.6 mg (0.1 mmol) of potassium iodide, 304 mg (2.2 mmol) of potassium carbonate, 287 mg (1 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 218 mg (63.5 %) of a colorless oil.

$[\alpha]_D^{20} = -62.5$ (c = 3.35, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.49-1.59 (m, 1 H, NCHCCH_2), 1.62-1.80 (m, 2 H, NCH_2CH_2), 1.94-2.05 (m, 1 H, NCHCCH_2), 2.11 (dt, *J* = 8.2/9.0 Hz, 1 H, NCH_2), 2.26 (dd, *J* = 14.9/9.0 Hz, 1 H, CH_2COO), 2.28-2.35 (m, 3 H, =CCH_2CH_2N), 2.60 (dd, *J* = 14.9/4.3 Hz, 1 H, CH_2COO), 2.70-2.79 (m, 1 H, NCHC), 2.80-2.88 (m, 1 H, =CCH_2CH_2N), 3.02 (ddd, *J* = 9.3/7.5/3.1 Hz, 1 H, NCH_2), 3.64 (s, 3 H, OCH_3), 6.10 (t, *J* = 7.0 Hz, 1 H, =CH), 7.16-7.40 (m, 10 H, aromat. H).

(g) (*R*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid methyl ester (R-28a)

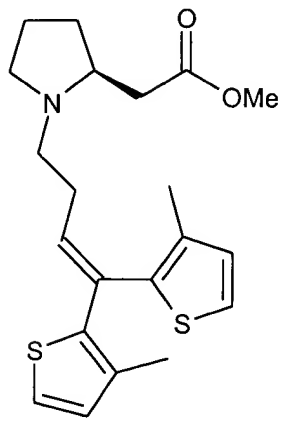


R-28a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 227 mg (0.82 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-ylacetic acid methyl ester (**R-21**, see Preparation Example 6), 13.6 mg (0.082 mmol) of potassium iodide, 113 mg (0.82 mmol) of potassium carbonate, 235 mg (0.82 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 47 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 175 mg (61.1 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28a**. $[\alpha]_D^{20} = +61.2$ (c = 1.49, $CHCl_3$).

(h) (*S*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid methyl ester (S-28b)



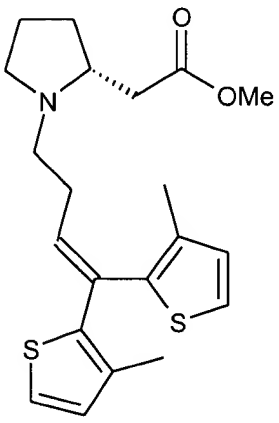
S-28b

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 179 mg (1.0 mmol) of (*S*)-pyrrolidin-2-yl acetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 16.6 mg (0.1 mmol) of potassium iodide, 276 mg (2.0 mmol) of potassium carbonate, 327 mg (1.0 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 159 mg (40.8 %) of a colorless oil.

$[\alpha]_D^{20} = -60.2$ (c = 0.99, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.49-1.57 (m, 1 H, NCH_2CH_2), 1.67-1.76 (m, 2 H, $NCH_2CH_2CH_2$), 1.96-2.03 (m, 1 H, $NCHCCH_2$), 2.02 (s, 3 H, $-CH_3$), 2.04 (s, 3 H, $-CH_3$), 2.13 (td, *J* = 8.7/8.4 Hz, 1 H, NCH_2), 2.25 (dd, *J* = 14.8/8.8 Hz, 1 H, CH_2COO), 2.28-2.36 (m, 3 H, $=CCH_2CH_2N$), 2.62 (dd, *J* = 14.8/4.4 Hz, 1 H, CH_2COO), 2.70-2.78 (m, 1 H, NCHC), 2.81-2.89 (m, 1 H, $=CCH_2CH_2N$), 3.04 (ddd, *J* = 10.0/7.4/3.3 Hz, 1 H, NCH_2), 3.66 (s, 3 H, $-OCH_3$), 6.06 (t, *J* = 7.0 Hz, 1 H, =CH), 6.77 (d, *J* = 5.2 Hz, 1 H, SC=CH), 6.84 (d, *J* = 5.2 Hz, 1 H, SC=CH), 7.06 (d, *J* = 5.2 Hz, 1 H, SCH=), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=).

(i) (*R*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid methyl ester (R-28b)



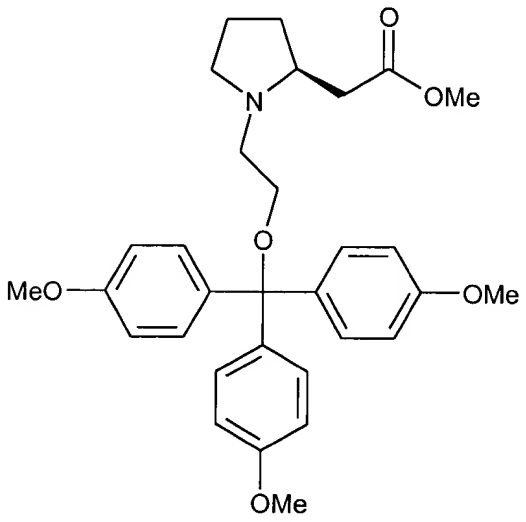
R-28b

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 277 mg (1.0 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-yl acetic acid methyl ester (**R-21**, see Preparation Example 6), 16.6 mg (1.0 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 327 mg (1 mmol) of 4,4-bis-(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 161 mg (41.3 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28b**.

$[\alpha]_D^{20} = +61.3$ (c = 1.04, $CHCl_3$).

(j) (*S*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid methyl ester (S-28c)



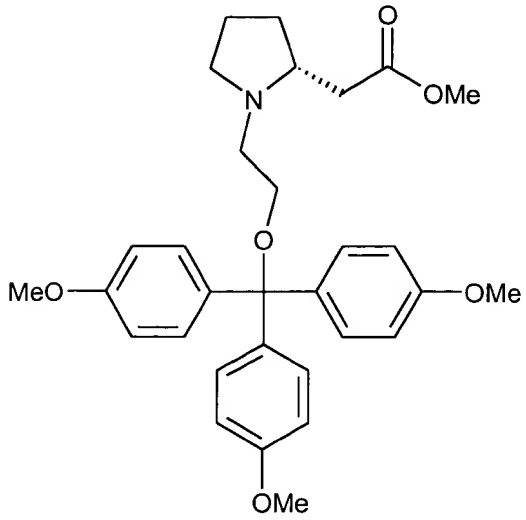
S-28c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure A: 215 mg (1.2 mmol) of (*S*)-pyrrolidin-2-ylacetic acid methyl ester hydrochloride (**S-19-HCl**, see Preparation Example 5), 19.9 mg (0.12 mmol) of potassium iodide, 332 mg (2.4 mmol) of potassium carbonate, 548 mg (1 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 7/3) afforded 220 mg (35.2 %) of a colorless oil.

$[\alpha]_D^{20} = -27.6$ (c = 1.77, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.49-1.59 (m, 1 H, NCH_2CH_2), 1.68-1.80 (m, 2 H, $NCH_2CH_2CH_2$), 1.97-2.07 (m, 1 H, $NCHCCH_2$), 2.21-2.31 (m, 2 H, CH_2COO, NCH_2), 2.51 (dt, *J* = 12.5/6.5 Hz, 1 H, OCH_2CH_2N), 2.65 (dd, *J* = 15.1/4.0 Hz, 1 H, CH_2COO), 2.79-2.87 (m, 1 H, NCHC), 2.97 (dt, *J* = 12.5/6.5 Hz, 1 H, OCH_2CH_2N), 3.06 (ddd, *J* = 10.4/7.1/3.5 Hz, 1 H, NCH_2), 3.20 (m, 2 H, OCH_2CH_2N), 3.67 (s, 3 H, $COOCH_3$), 3.81 (s, 9 H, $-OCH_3$), 6.81-6.87 (m, 6 H, aromat. H), 7.34-7.39 (m, 6 H, aromat. H).

(k) (*R*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid methyl ester (R-28c)

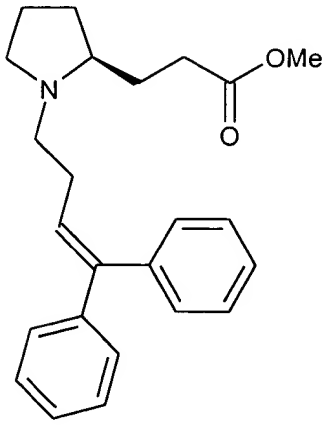


R-28c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 227 mg (0.82 mmol) of (*R*)-1-benzyloxycarbonylpyrrolidin-2-ylacetic acid methyl ester (**R-21**, see Preparation Example 6), 13.6 mg (0.082 mmol) of potassium iodide, 113 mg (0.82 mmol) of potassium carbonate, 375 mg (0.82 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 45 h. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-28c**. Purification by column chromatography (petrol ether/ethyl acetate = 20/80) afforded 175 mg (41.1 %) of a colorless oil. $[\alpha]_D^{20} = +26.7$ (c = 1.5, $CHCl_3$).

(l) 3-[(*S*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl] propionic acid methyl ester (S-29a)



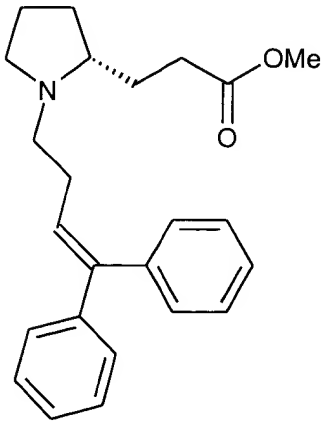
S-29a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 269 mg (0.93 mmol) of **S-24** (see Preparation Example 9), 15.4 mg (0.093 mmol) of potassium iodide, 128 mg (0.93 mmol) of potassium carbonate, 267 mg (0.93 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 48 h. Purification by column chromatography (*n*-hexane/ether = 7/3) afforded 142 mg (42.0 %) of a colorless oil.

$[\alpha]_D^{20}$ = – 63.9 (c = 1.1, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.30-1.39 (m, 1 H, NCHCCH_2), 1.47-1.70 (m, 3 H, CH_2CH$_2$COO, NCH$_2$CH_2), 1.75-1.83 (m, 1 H, NCHCCH_2), 1.83-1.93 (m, 1 H, CH_2CH$_2$COO), 1.99 (td, *J* = 9.0/8.2 Hz, 1 H, NCH$_2$), 2.11-2.28 (m, 5 H, =CCH_2CH_2N, CH$_2$COO, NCHC), 2.33 (ddd, *J* = 15.6/9.5/5.9 Hz, 1 H, CH$_2$COO), 2.84 (ddd, *J* = 15.3/8.5/6.1 Hz, 1 H, =CCH$_2$CH_2N), 2.97 (ddd, *J* = 9.0/7.4/2.9 Hz, 1 H, NCH$_2$), 3.59 (s, 3 H, OCH$_3$), 6.05 (t, *J* = 7.3 Hz, 1 H, =CH), 7.10-7.33 (m, 10 H, aromat. H).

(m) 3-[(*R*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid methyl ester (R-29a)

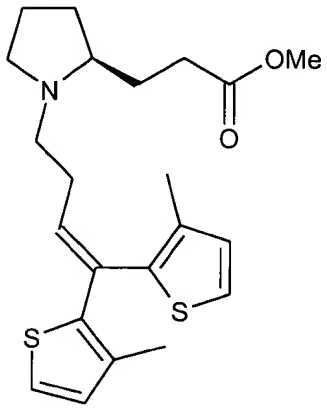


R-29a

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 231 mg (0.8 mmol) **R-24** (see Preparation Example 10), 13.3 mg (0.08 mmol) of potassium iodide, 111 mg (0.8 mmol) of potassium carbonate, 230 mg (0.8 mmol) of 4,4-diphenylbut-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (*n*-hexane/ether = 3/7) afforded 131 mg (45.0 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29a**. $[\alpha]_D^{20} = +63.55$ (c = 1.07, $CHCl_3$).

(n) 3-{(*S*)-1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}propionic acid methyl ester (S-29b)

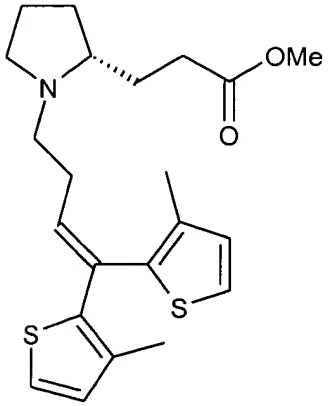


S-29b

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **S-24** (see Preparation Example 9), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 327 mg (1.0 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 46 h. Purification by column chromatography (petrol ether/ethyl acetate = 5/5) afforded 165 mg (40.9 %) of a colorless oil. $[\alpha]_D^{20} = -6.2$ (c = 1.05, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.37-1.47 (m, 1 H, NCHCCH_2), 1.53-1.78 (m, 3 H, CH_2CH$_2$COO, NCH$_2$CH_2), 1.82-1.90 (m, 1 H, NCHCCH_2), 1.91-2.01 (m, 1 H, CH_2CH$_2$COO), 2.03 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 2.07 (q, *J* = 8.9 Hz, 1 H, NCH_2), 2.18-2.35 (m, 5 H, =CCH_2CH_2N, CH_2COO, NCHC), 2.40 (ddd, *J* = 15.6/9.5/5.9 Hz, 1 H, CH_2COO), 2.91 (dt, *J* = 11.4/8.1 Hz, 1 H, =CCH$_2$CH_2N), 3.07 (ddd, *J* = 9.5/7.5/3.0 Hz, 1 H, NCH_2), 3.68 (s, 3 H, OCH_3), 6.09 (t, *J* = 7.3 Hz, 1 H, =CH), 6.77 (d, *J* = 5.2 Hz, 1 H, SC=CH), 6.85 (d, *J* = 5.2 Hz, 1 H, SC=CH), 7.06 (d, *J* = 5.2 Hz, 1 H, SCH=), 7.21 (d, *J* = 5.2 Hz, 1 H, SCH=).

(o) 3-{(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}propionic acid methyl ester (R-29b)

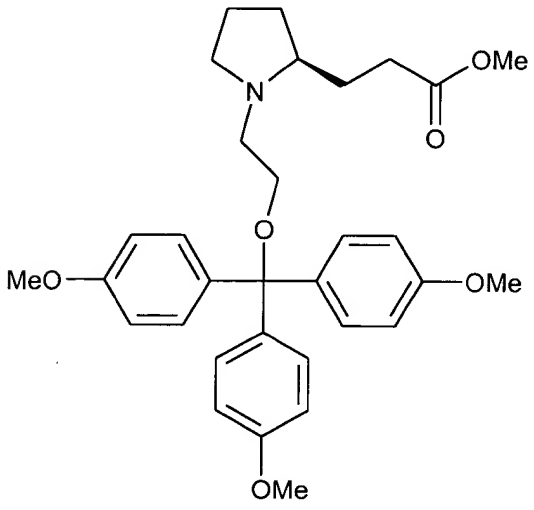


R-29b

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 474 mg (1.64 mmol) of **R-24** (see Preparation Example 10), 27.2 mg (0.16 mmol) of potassium iodide, 227 mg (1.64 mmol) of potassium carbonate, 536 mg (1.64 mmol) of 4,4-bis(3-methyl-2-thienyl)but-3-en-1-yl bromide. Reaction time: 47 h. Purification by column chromatography (petrol ether/ethyl acetate = 5/5) afforded 260 mg (39.4 %) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29b**. $[\alpha]_D^{20} = +6.3$ (c = 1.18, $CHCl_3$).

(p) 3-[(*S*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid methyl ester (S-29c)

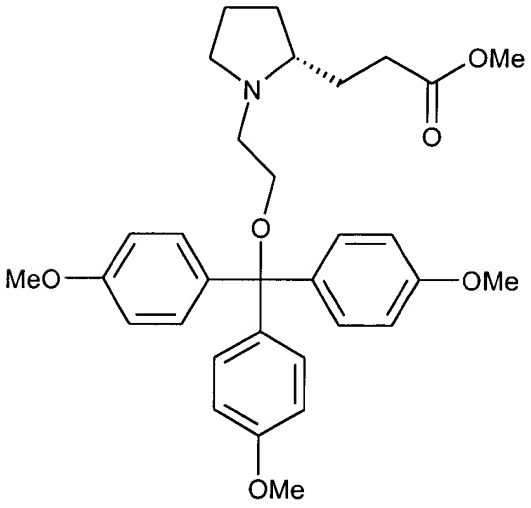


S-29c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **S-24** (see Preparation Example 9), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 457 mg (1.0 mmol) of **R-Br c** (see Preparation Example 13). Reaction time: 48 h. Purification by column chromatography (petrol ether/ ethyl acetate = 2/8) afforded 117 mg (21.9 %) of a colorless oil. $[\alpha]_D^{20} = -29.5$ (c = 1.27, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.36-1.46 (m,1 H, NCH_2CH_2), 1.56-1.64 (m, 1 H, CH_2CH_2COO), 1.64-1.73 (m, 2 H, $NCH_2CH_2CH_2$), 1.81-1.89 (m, 1 H, $NCHCCH_2$), 1.90-2.00 (m, 1 H, CH_2CH_2COO), 2.15 (q, J = 9.0 Hz, 1 H, NCH_2), 2.21-2.47 (m, 4 H, CH_2COO, OCH_2CH_2N, NCHC), 2.98-3.10 (m, 2 H, OCH_2CH_2N, NCH_2), 3.12-3.25 (m, 2 H, OCH_2CH_2N), 3.67 (s, 3 H, $COOCH_3$), 3.80 (s, 9 H, OCH_3), 6.80-6.85 (m, 6 H, aromat. H), 7.33-7.37 (m, 6 H, aromat. H).

(q) 3-[(*R*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid methyl ester (R-29c)



R-29c

N-Alkylation of the pyrrolidinylalkanecarboxylic acid alkyl esters:

General Procedure B: 289 mg (1.0 mmol) of **R-24** (see Preparation Example 10), 16.6 mg (0.1 mmol) of potassium iodide, 138 mg (1.0 mmol) of potassium carbonate, 457 mg (1.0 mmol) of **R-Br c** (see Preparation Example 13),. Reaction time: 48 h. Purification by

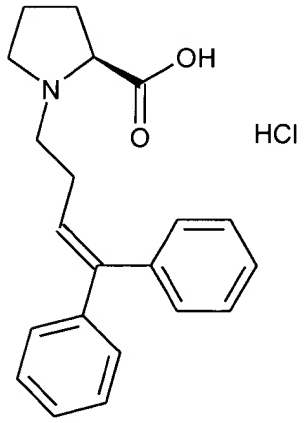
column chromatography (petrol ether/ethyl acetate = 2/8) afforded 239 mg (44.8%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-29c** . $[\alpha]_D^{20} = +29.5$ (c = 1.05, $CHCl_3$).

Example 2

(a) Saponification of the methyl esters, general procedure

The methyl esters (= 1 equiv.) each were dissolved in ethanol (about 2 ml / mmol). The solution was cooled to 0 °C, and 12 N NaOH (2 equiv.) was added dropwise thereto. Then the cooling bath was removed and the reaction mixture was stirred at RT for the indicated period of time. Thereafter the reacton mixture was again cooled to 0 °C and, if not stated otherwise, acidified to pH ≈ 6 by dropwise addition of 0.25 N HCl. The reaction mixture was taken up in CH_2Cl_2 and water and extracted five times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), concentrated i. vac., and the obtained residue was treated further as indicated.

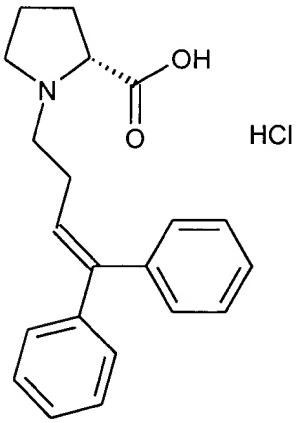
(b) (*S*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid hydrochloride (S-30a)



S-30a

Saponification of methyl ester, General Procedure: 265 mg (0.79 mmol) of **S-27a** (see Example 1(b)), 132 µl of 12 M NaOH, reaction time 5 h. The work-up was conducted in deviation from the General Procedure by dropwise acidification with cooling with 4 M HCl to pH ≈ 1 and five extractions with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$), concentrated i. vac., and the obtained hydrochloride was recrystallized from ethanol. Yield: 231 mg (81.9%); colorless crystals, m.p.: 220 °C. – $[\alpha]_D^{20}$ = – 21.0 (c = 1.00, CH_3OH). – ^1H NMR (CD_3OD, 20 °C): δ = 1.88-2.00 (m, 1 H, NCH_2CH_2), 2.08-2.21 (m, 2 H, $NCH_2CH_2CH_2$), 2.43-2.53 (m, 1 H, $NCHCCH_2$), 2.54-2.62 (m, 2 H, $=CHCH_2$), 3.05-3.14 (m, 1 H, NCH_2), 3.20-3.30 (m, 1 H, $=CHCH_2CH_2$), 3.45 (td, *J* = 12.4/8.0 Hz, 1 H, $=CHCH_2CH_2$), 3.62 (ddd, *J* = 12.4/7.5/4.0 Hz, 1 H, NCH_2), 4.08 (dd, *J* = 9.6/6.8 Hz, 1 H, NCHC), 6.11 (t, *J* = 7.3 Hz, 1 H, =CH), 7.19-7.49 (m, 10 H, aromat. H).

(c) (*R*)-N-(4,4-Diphenylbut-3-en-1-yl)pyrrolidine-2-carboxylic acid hydrochloride (R-30a)

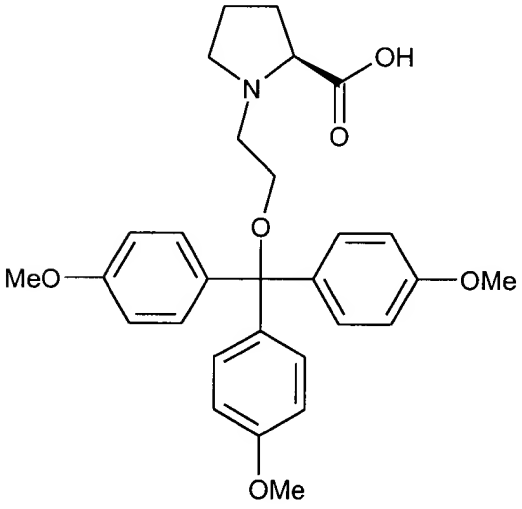


R-30a

Saponification of methyl ester, General Procedure: 210 mg (0.63 mmol) **R-27a** (see Example 1(c)), 105 µl of 12 M NaOH, reaction time 5 h. The work-up was conducted in deviation from the General Procedure by dropwise acidification with cooling with 4 M HCl to pH ≈ 1 and five extractions with CH_2Cl_2. The combined organic phases were

dried ($MgSO_4$), concentrated i. vac., and the obtained hydrochloride was recrystallized from ethanol.. Yield: 184 mg (82.1%); colorless crystals, m.p.: 218 °C. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-30a**. – $[\alpha]_D^{20}$ = + 21.9 (c = 0.71, CH_3OH).

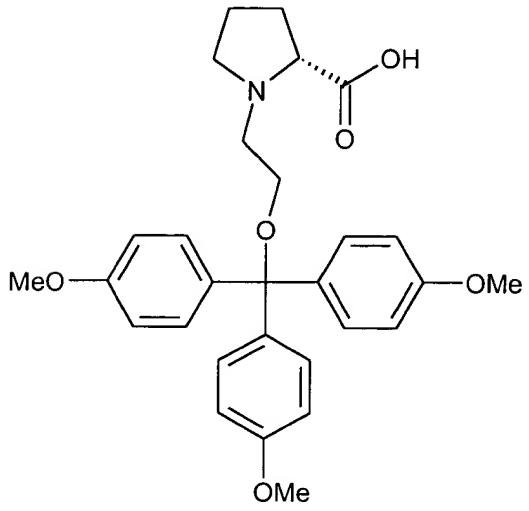
(d) (*S*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid (S-30c)



S-30c

Saponification of methyl ester, General Procedure: 289 mg (0.63 mmol) **S-27c** (see Example 1(d)), 95 µl of 12 M NaOH, reaction time 4 h. Recrystallization from ether/*n*-pentane (1/1) afforded 225 mg (80.1%) of colorless crystals, m.p.: 69-75 °C (decomposition). – $[\alpha]_D^{20}$ = = – 8.2 (c = 4.92, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.85-1.95 (m, 2 H, NCH_2CH_2), 2.22 (q, *J* = 7.3 Hz, 2 H, $NCHCCH_2$), 2.77 (dt, *J* = 9.8/8.8 Hz, 1 H, NCH_2), 2.93-3.01 (m, 1 H, OCH_2CH_2N), 3.27-3.36 (m, 2 H, OCH_2CH_2N), 3.39-3.47 (m, 1 H, OCH_2CH_2N), 3.54 (dt, *J* = 9.8/5.5 Hz, 1 H, NCH_2), 3.68-3.76 (m, 1 H, NCHC), 3.80 (s, 9 H, OCH_3), 6.80-6.86 (m, 6 H, aromat. H), 7.28-7.33 (m, 6 H, aromat. H).

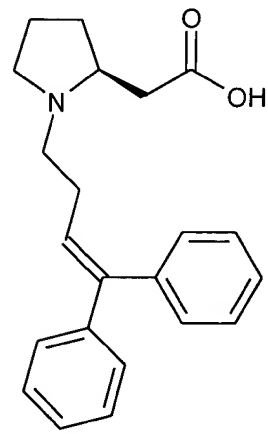
(e) (*R*)-N-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidine-2-carboxylic acid (R-30c)



R-30c

Saponification of methyl ester, General Procedure: 243 mg (0.48 mmol) of **R-27c** (see Example 1(e)), 80 µl of 12 M NaOH, reaction time 4 h. Recrystallization from ether/*n*-pentane (1/1) afforded 186 mg (78.8%) of colorless crystals, m.p.: 69-75 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-30c** $[\alpha]_D^{20} = +8.1$ (c = 2.73, $CHCl_3$).

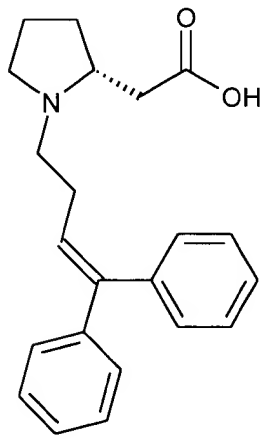
(f) (*S*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid (S-31a)



S-31a

Saponification of methyl ester, General Procedure: 139 mg (0.398 mmol) of **S-28a** (see Example 1(f)), 66 µl of 12 M NaOH, reaction time 5 h. CC (CH_2Cl_2/ethanol = 8/2) afforded 110 mg (82.5%) of colorless crystals, m.p.: 130-137 °C (decomposition). – $[\alpha]_D^{20} = -85.4$ (c = 1.30, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.67-1.94 (m, 3 H, $NCH_2CH_2CH_2$), 2.05-2.15 (m, 1 H, $NCHCCH_2$), 2.35 (td, *J* =10.5/8.5 Hz, 1 H, NCH_2), 2.42-2.54 (m, 4 H, $=CCH_2CH_2N$, CH_2COO), 2.65 (dd, *J* =17.1/5.1 Hz, 1 H, CH_2COO), 2.95-3.04 (m, 1 H, NCHC), 3.06-3.16 (m, 1 H, $=CCH_2CH_2N$), 3.19 (ddd, *J* = 10.5/7.1/3.9 Hz, 1 H, NCH_2), 6.02 (t, *J* = 7.3 Hz, 1 H, =CH), 7.14-7.44 (m, 10 H, aromat. H).

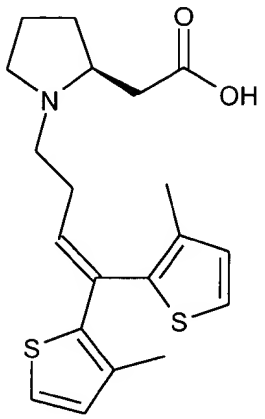
(g) (*R*)-[1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]acetic acid (R-31a)



R-31a

Saponification of methyl ester, General Procedure: 136 mg (0.389 mmol) of **R-28a** (see Example 1(g)), 65 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 105 mg (80.4%) of colorless crystals, m.p.: 129-135 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31a**. $[\alpha]_D^{20} = +86.5$ (c = 0.47, $CHCl_3$).

(h) (*S*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid (S-31b)

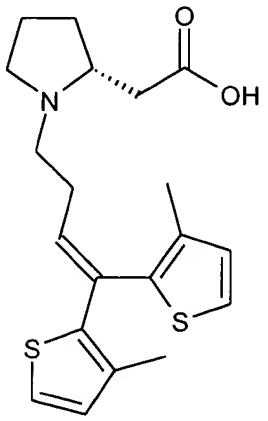


S-31b

Saponification of methyl ester, General Procedure: 85 mg (0.218 mmol) of **S-28b** (see Example 1(h)), 36 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 57 mg (69.6%) of a colorless oil.

$[\alpha]_D^{20} = -64.9$ (c = 0.85, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.66-1.79 (m, 1 H, NCH_2CH_2), 1.79-1.95 (m, 2 H, $NCH_2CH_2CH_2$), 1.98 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.04-2.17 (m, 1 H, $NCHCCH_2$), 2.38-2.55 (m, 5 H, $=CCH_2CH_2N$, CH_2COO, NCH_2), 2.63 (dd, *J* = 16.9/5.3 Hz, 1 H, CH_2COO), 2.93-3.01 (m, 1 H, NCHC), 3.03-3.12 (m, 1 H, $=CCH_2CH_2N$), 3.29 (ddd, *J* = 11.0/7.5/4.0 Hz, 1 H, NCH_2), 6.01 (t, *J* = 7.3 Hz, 1 H, =CH), 6.76 (d, *J* = 5.1 Hz, 1 H, SC=CH), 6.87 (d, *J* = 5.1 Hz, 1 H, SC=CH), 7.06 (d, *J* = 5.1 Hz, 1 H, SCH=), 7.24 (d, *J* = 5.1 Hz, 1 H, SCH=).

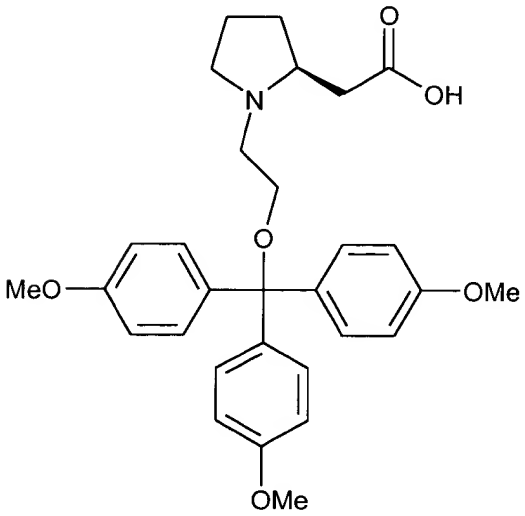
(i) (*R*)-{1-[4,4-Bis(3-methyl-2-thienyl)but-3-en-1-yl]pyrrolidin-2-yl}acetic acid (R-31b)



R-31b

Saponification of methyl ester, General Procedure: 105 mg (0.27 mmol) of **R-28b** (see Example 1(i)), 45 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 69 mg (68.1%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31b**. $[\alpha]_D^{20} = +65.2$ (c = 1.02, $CHCl_3$).

(j) (*S*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid (S-31c)

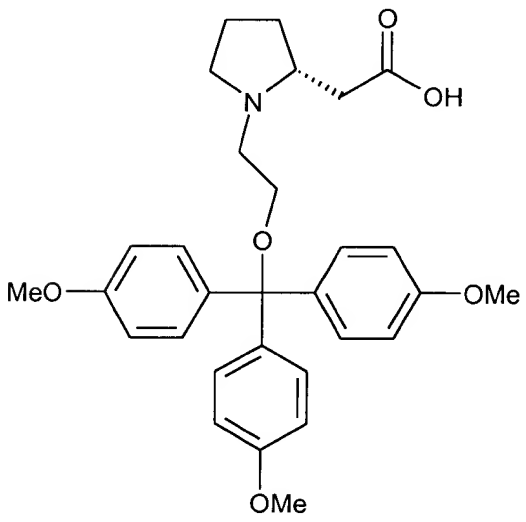


S-31c

Saponification of methyl ester, General Procedure: 220 mg (0.423 mmol) of **S-28c** (see Example 1(j)), 70 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 176 mg (82.2%) of colorless crystals, m.p.: 68-73 °C (decomposition).

$[\alpha]_D^{20}$ = – 32.0 (c = 0.66, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.69-1.97 (m, 3 H, $NCH_2CH_2CH_2$), 2.04-2.15 (m, 1 H, $NCHCCH_2$), 2.44-2.59 (m, 3 H, OCH_2CH_2N, NCH_2, CH_2COO), 2.68 (dd, *J* = 17.2/4.3 Hz, 1 H, CH_2COO), 2.98-3.07 (m, 1 H, NCHC), 3.07-3.17 (m, 1 H, OCH_2CH_2N), 3.26-3.44 (m, 3 H, OCH_2CH_2N, NCH_2), 3.79 (s, 9 H, OCH_3), 6.84-6.86 (m, 6 H, aromat. H), 7.28-7.34 (m, 6 H, aromat. H).

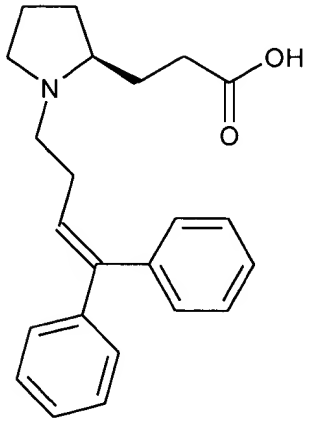
(k) (*R*)-(1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl)acetic acid (R-31c)



R-31c

Saponification of methyl ester, General Procedure: 135 mg (0.26 mmol) of **R-28c** (see Example 1(k)), 43 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 109 mg (83.0%) of colorless crystals, m.p.: 68-73 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-31c**. $[\alpha]_D^{20}$ = + 32.7 (c = 1.02, $CHCl_3$).

(l) **3-[(*S*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid (S-32a)**

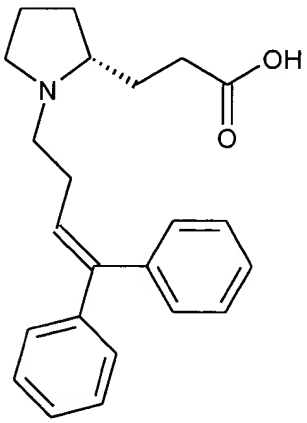


S-32a

Saponification of methyl ester, General Procedure: 122 mg (0.336 mmol) of **S-29a** (see Example 1(l)), 56 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 88 mg (75.0%) of a colorless oil.

$[\alpha]_D^{20} = -20.4$ (c = 1.10, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.61-1.72 (m, 1 H, NCH_2CH_2), 1.72-1.90 (m, 4 H, CH_2CH_2COO, $NCH_2CH_2CH_2$), 1.90-2.02 (m, 1 H, $NCHCCH_2$), 2.32-2.59 (m, 6 H, $=CCH_2CH_2N$, NCH_2, CH_2COO), 2.85-2.94 (m, 1 H, NCHC), 3.05 (td, J =11.0/5.0 Hz, 1 H, $=CCH_2CH_2N$), 3.18-3.25 (m,1 H, NCH_2), 6.03 (t, J = 7.0 Hz, 1 H, =CH), 7.12-7.40 (m, 10 H, aromat. H).

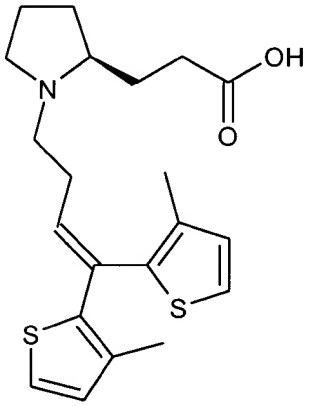
(m) 3-[(*R*)-1-(4,4-Diphenylbut-3-en-1-yl)pyrrolidin-2-yl]propionic acid (R-32a)



R-32a

Saponification of methyl ester, General Procedure: 107 mg (0.336 mmol) of **R-29a** (see Example 1(m)), 49 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 76 mg (73.9%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32a**. $[\alpha]_D^{20} = +19.5$ (c = 0.87, $CHCl_3$).

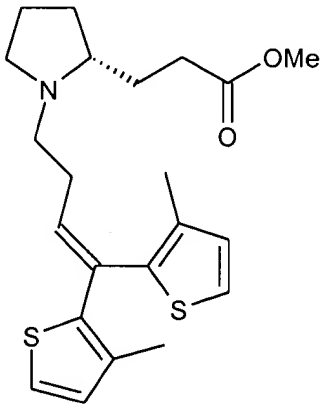
(n) 3-{(*S*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]pyrrolidin-2-yl}propionic acid (S-32b)



S-32b

Saponification of methyl ester, General Procedure: 100 mg (0.248 mmol) of **S-29b** (see Example 1(n)), 41 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 68 mg (70.5%) of a colorless oil. $[\alpha]_D^{20} = -17.0$ (c = 0.73, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.70-1.85 (m, 2 H, $NCH_2CH_2CH_2$), 1.85-2.10 (m, 4 H, CH_2CH_2COO, $NCH_2CH_2CH_2$), 1.96 (s, 3 H, CH_3), 2.00 (s, 3 H, CH_3), 2.40-2.75 (m, 5 H, $=CCH_2CH_2N$, NCH_2, CH_2COO), 2.69 (td, *J*=11.3/5.0 Hz, 1 H, $=CCH_2CH_2N$), 3.03-3.15 (m, 2 H, $=CCH_2CH_2N$, NCHC), 3.28-3.38 (m, 1 H, NCH_2), 5.96 (t, *J* = 7.3 Hz, 1 H, =CH), 6.74 (d, *J* = 4.4 Hz, 1 H, SC=CH), 6.85 (d, *J* = 4.4 Hz, 1 H, SC=CH), 7.05 (d, *J* = 4.4 Hz, 1 H, SCH=), 7.22 (d, *J* = 4.4 Hz, 1 H, SCH=).

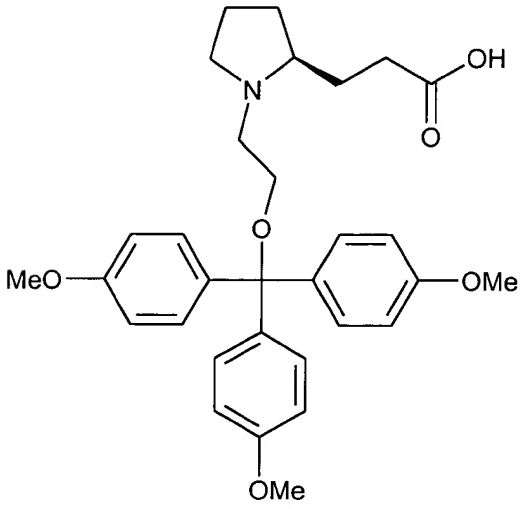
(o) 3-{(*R*)-1-[4,4-Bis(3-methyl-2-thienyl)-3-butenyl]pyrrolidin-2-yl}propionic acid (R-32b)



R-32b

Saponification of methyl ester, General Procedure: 170 mg (0.421 mmol) of **R-29b** (see Example 1(o)), 70 µl of 12 M NaOH, reaction time 5 h. CC (ethanol) afforded 112 mg (68.3%) of a colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32b**. $[\alpha]_D^{20} = +17.3$ (c = 0.91, $CHCl_3$).

(p) 3-[(*S*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid (S-32c)

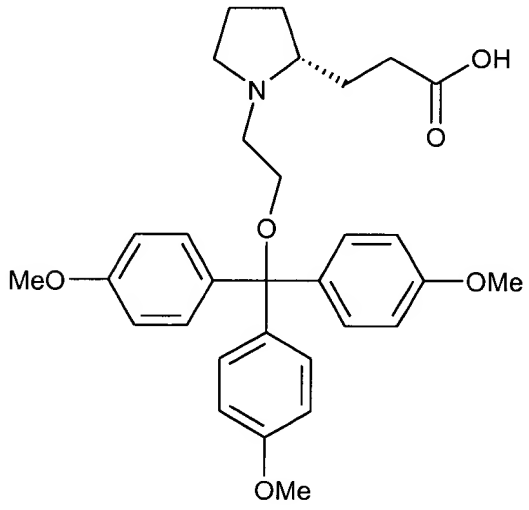


S-32c

Saponification of methyl ester, General Procedure: 93 mg (0.174 mmol) of **S-29c** (see Example 1(p)), 29 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-

pentane (1/1) afforded 73 mg (80.6%) colorless crystals, m.p.: 65-73 °C (decomposition). $[\alpha]_D^{20} = -4.4$ (c = 0.51, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.73-2.07 (m, 6 H, CH_2CH_2COO, $NCH_2CH_2CH_2$), 2.36-2.46 (m, 1 H, CH_2COO), 2.50-2.60 (m, 1 H, CH_2COO), 2.72-3.81 (m, 2 H, OCH_2CH_2N, NCH_2), 3.03-3.12 (m, 1 H, NCHC), 3.18-3.28 (m, 1 H, OCH_2CH_2N), 3.40-3.50 (m,1 H, NCH_2), 3.49-3.61 (m, 2 H, OCH_2CH_2N), 3.70 (s, 9 H, OCH_3), 6.78-6.86 (m, 6 H, aromat. H), 7.23-7.35 (m, 6 H, aromat. H).

(q) 3-[(*R*)-1-{2-[Tris(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]propionic acid (R-32c)

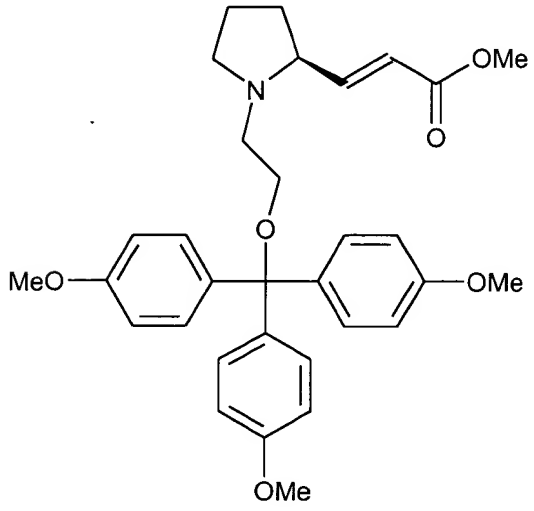


R-32c

Saponification of methyl ester, General Procedure: 143 mg (0.268 mmol) of **R-29c** (see Example 1(q)), 45 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 115 mg (82.6%) of colorless crystals, m.p.: 64-72 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-32c**. $[\alpha]_D^{20} = +4.1$ (c = 0.50, $CHCl_3$).

Example 3

(a) (*E*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (S-34)



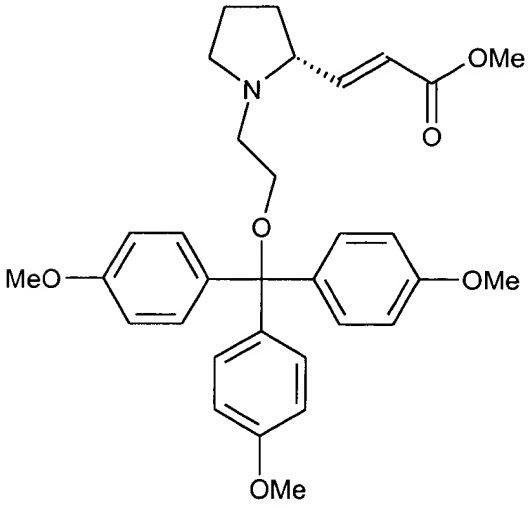
S-34

To a solution of 295 mg (0.584 mmol) of **S-27c** (see Example 1(d)) in 4 ml of toluene there was added dropwise at -60 °C over a period of 10 min 1.4 ml (2.4 equiv.) of DIBAH solution (1 M in *n*-hexane), and the reaction mixture was stirred for 2 h at -60 °C. Thereafter the reaction was stopped by dropwise addition of 0.5 ml of methanol, heated to RT and taken up in water and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. The oily residue (275 mg) was dissolved in 2.5 ml of acetonitrile and 30 mg (0.7 mmol, 1.2 equiv.) of LiCl and 123 µl (0.7 mmol, 1.2 equiv.) of DIPEA were added thereto. Thereafter 113 µl (0.7 mmol, 1.2 equiv.) of trimethylphosphono acetate was added dropwise. The reaction mixture was stirred for 16 h at RT, then concentrated i. vac., taken up in Et_2O and water, and the aqueous phase was extracted three times with Et_2O. The combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. Two CCs (*n*-hexane/ ether = 1/1) afforded 180 mg (58.0%) of a colorless oil.

$[\alpha]_D^{20}$ = – 32.9 (c = 0.99, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.53-1.66 (m, 1 H, NCHCCH_2), 1.69-1.87 (m, 2 H, NCH_2CH_2), 1.90-2.02 (m, 1 H, NCHCCH_2), 2.25 (q, *J* =

8.6 Hz, 1 H, NCH_2), 2.41 (dt, J = 12.9/5.8 Hz, 1 H, OCH_2CH_2N), 2.86-3.02 (m, 2 H, OCH_2CH_2N, NCHC), 3.07-3.24 (m, 3 H, OCH_2CH_2N, NCH_2), 3.74 (s, 3 H, $COOCH_3$), 3.78 (s, 9 H, OCH_3), 5.98 (d, J = 15.6 Hz, 1 H, =CHCOO), 6.78-6.87 (m, 7 H, CH=, aromat. H), 7.31-7.37 (m, 6 H, aromat. H).

(b) (*E*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (R-34)

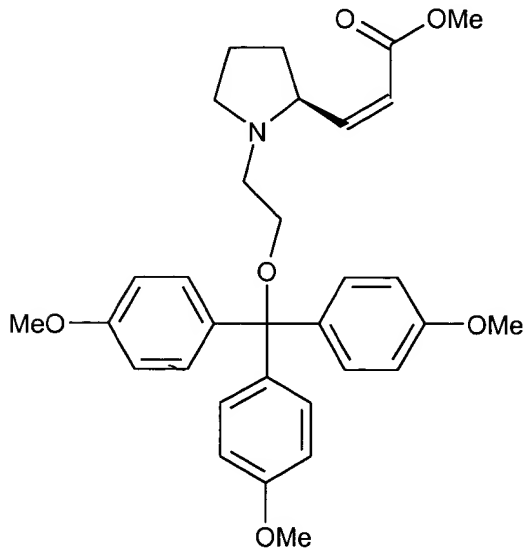


R-34

The synthesis of the compound was conducted according to the procedure for **S-34**.
Batch size: 308 mg (0.594 mmol) of **R-27c** (see Example 1(e)); 1.43 ml of DIBAH solution (1 M in *n*-hexane); 30 mg (0.7 mmol, 1.2 equiv.) of LiCl; 125 µl (0.71 mmol, 1.2 equiv.) of DIPEA; 115 µl (0.71 mmol, 1.2 equiv.) of trimethylphosphono acetate. Yield: 181 mg (59.5%); colorless oil. The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-34** . $[\alpha]_D^{20}$ = + 33.6 (c = 1.0, $CHCl_3$).

Example 4

(a) (*Z*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (S-35)

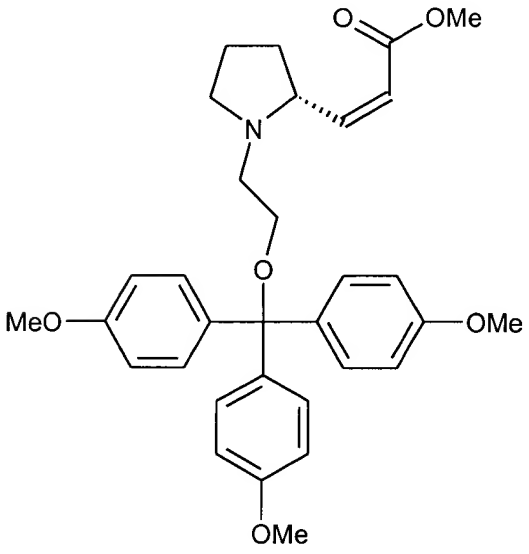


S-35

To a solution of 437 mg (0.865 mmol) of **S-27c** (see Example 1(d)) in 6 ml of toluene there was added dropwise at -60 °C and over a period of 10 min 2.1 ml (2.4 equiv.) DIBAH solution (1 M in *n*-hexane), and the reaction mixture was stirred for 2 h at -60 °C. Then the reaction was stopped by dropwise addition of 0.5 of methanol, heated to RT and taken up in water and Et_2O. The aqueous phase was extracted three times with Et_2O, the combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. The oily residue (410 mg) was dissolved in 5 ml of THF and added dropwise at -78 °C to a solution, prepared at -78 °C, of 1.143 g (5 equiv.) of crown ether (18-crown-6), 183 µl of (1 equiv.) of bis(3,3,3-trifluoroethoxy)phosphonic acid methyl ester and 1.15 ml (1 equiv.) of $KN(TMS)_2$ (15% solution in toluene) in 5 ml of THF. The reaction mixture was stirred for 1 h at RT, the reaction was stopped by addition of 1 ml of saturated NH_4Cl solution, taken up in CH_2Cl_2 and water, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated i. vac.. Several CCs (*n*-hexane/ether = 1/1) afforded 197 mg (43.0%) of **S-35** as colorless oil. Additionally 66 mg (14.3%) of **S-34** could be isolated as colorless oil.

$[\alpha]_D^{20} = +9.6$ (c = 0.54, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.42-1.55 (m, 1 H, NCHCCH_2), 1.73-1.88 (m, 2 H, NCH_2CH_2), 2.05-2.16 (m, 1 H, NCHCCH_2), 2.25 (q, J = 8.9 Hz, 1 H, NCH_2), 2.49 (dt, J = 12.6/6.3 Hz, 1 H, OCH_2CH_2N), 2.87 (dt, J = 12.6/6.3 Hz, 1 H, OCH_2CH_2N), 3.10-3.24 (m, 3 H, OCH_2CH_2N, NCH_2), 3.70 (s, 3 H, $COOCH_3$), 3.78 (s, 9 H, OCH_3), 4.01 (q, J = 8.0 Hz, 1 H, NCHC), 5.80 (d, J = 11.6 Hz, 1 H, =CHCOO), 6.18 (dd, J = 11.6/8.0 Hz, 1 H, CH=), 6.76-6.85 (m, 6 H, aromat. H), 7.29-7.38 (m, 6 H, aromat. H).

(b) (*Z*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid methyl ester (R-35)



R-35

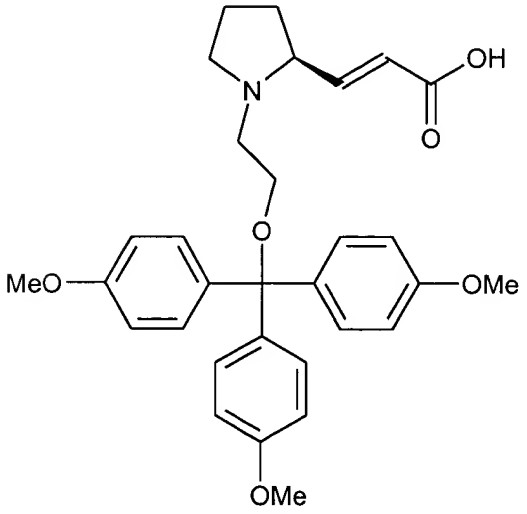
The synthesis of the compound was conducted according to the procedure for **S-35**.

Batch size: 259 mg (0.513 mmol) of **R-27c** (see Example 1(e)); 1.23 ml of DIBAH solution (1 M in *n*-hexane); 678 mg (5 equiv.) of crown ether (18-crown-6), 108 µl (1 equiv.) of bis(3,3,3-trifluoroethoxy)phosphonic acid methyl ester and 682 µl (1 equiv.) of $KN(TMS)_2$ (15% solution in toluene).

Yield: 116 mg (42.2%) of **R-35** as colorless oil, as well as 39 mg (14.3%) of **R-34**. The analytical data of the compound is in agreement with those of the enantiomers. $[\alpha]_D^{20} = -9.1$ (c = 0.50, $CHCl_3$).

Example 5

(a) (*E*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl] acrylic acid (S-36)

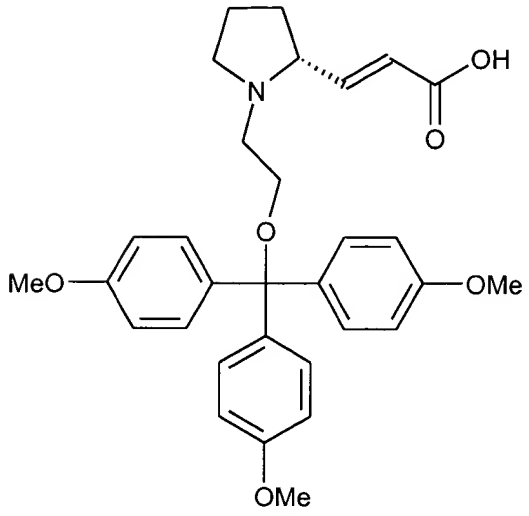


S-36

Saponification of methyl ester, general procedure: 157 mg (0.296 mmol) of **S-34** (see Example 3(a)), 49 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 120 mg (78.5%) of colorless crystals, m.p.: 78-86 °C (decomposition).

$[\alpha]_D^{20} = -15.6$ (c = 0.82, $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.67-1.80 (m, 2 H, $NCH_2CH_2CH_2$), 1.85-1.98 (m, 2 H, $NCH_2CH_2CH_2$), 2.49-2.59 (m, 2 H, OCH_2CH_2N, NCH_2), 3.04-3.18 (m, 2 H, OCH_2CH_2N, NCH_2), 3.23-3.37 (m, 2 H, OCH_2CH_2N), 3.60-3.68 (m, 1 H, NCHC), 3.70 (s, 9 H, OCH_3), 5.85 (d, *J* = 15.2 Hz, 1 H, =CHCOO), 6.67 (dd, *J* = 15.2/8.9 Hz, 1 H, C*H*=CHCOO), 6.71-6.76 (m, 6 H, aromat. H), 7.21-7.25 (m, 6 H, aromat. H).

(b) (*E*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (R-36)

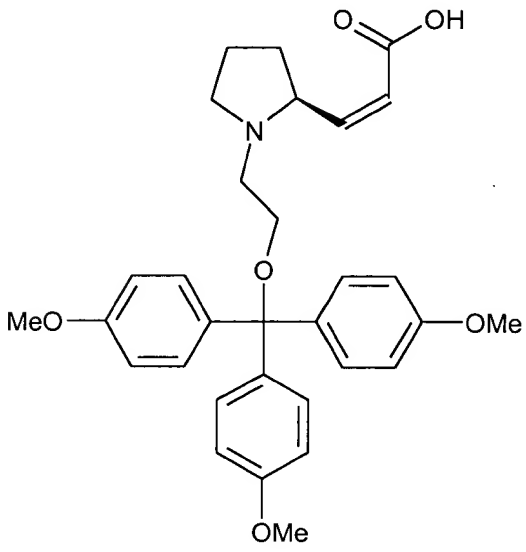


R-36

Saponification of methyl ester, General Procedure: 202 mg (0.38 mmol) of **R-34** (see Example 3(a)), 63 µl of 12 M NaOH, reaction time 5 h. Recrystallization from ether/*n*-pentane (1/1) afforded 156 mg (79.3%); colorless crystals, m.p.: 78-86 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-36**. $[\alpha]_D^{20} = +16.2$ (c = 3.31, $CHCl_3$).

Example 6

(a) (*Z*)-3-[(2*S*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (S-37)

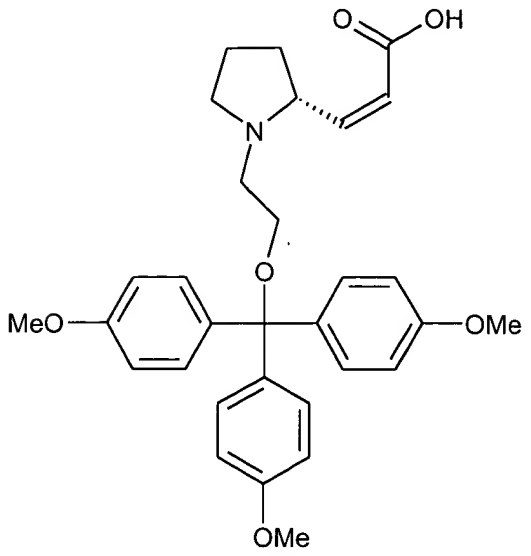


S-37

Saponification of methyl ester, general procedure: 85 mg (0.16 mmol) **of S-35** (see Example 4(a)), 27 µl of 12 M NaOH, reaction time 23 h. Recrystallization from ether/*n*-pentane (1/1) afforded 61 mg (73.7%); colorless crystals, m.p.: 100-105 °C (decomposition).

$[\alpha]_D^{20} = -12.7$ (c = 1.30, $CHCl_3$). – ^{1}H NMR ($CDCl_3$, 20 °C): δ = 1.82-1.95 (m, 2 H, $NCH_2CH_2CH_2$), 1.98-2.10 (m, 1 H, NCH_2CH_2), 2.18-2.27 (m, 1 H, $NCHCCH_2$), 2.59-2.71 (m, 2 H, NCH_2, OCH_2CH_2N), 3.06 (dt, *J* = 13.2/5.5 Hz, 1 H, NCH_2), 3.39-3.50 (m, 4 H, OCH_2CH_2N, NCH_2, NCHC), 3.79 (s, 9 H, OCH_3), 5.99-6.09 (m, 2 H, CH=CH), 6.78-6.85 (m, 6 H, aromat. H), 7.24-7.32 (m, 6 H, aromat. H).

(b) (*Z*)-3-[(2*R*)-1-{2-[Tris-(4-methoxyphenyl)methoxy]ethyl}pyrrolidin-2-yl]acrylic acid (R-37)

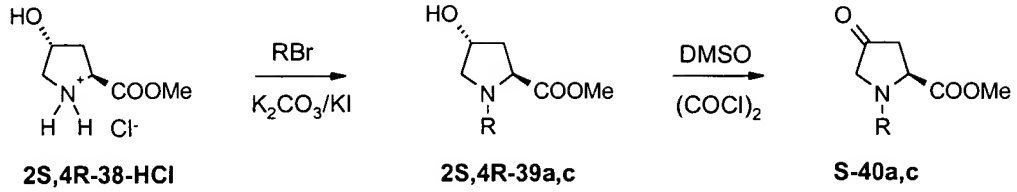


R-37

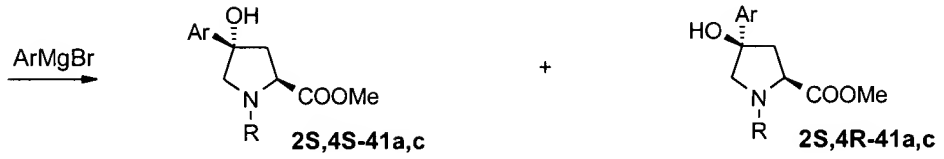
Saponification of methyl ester, general procedure: 91 mg (0.17 mmol) of **R-35** (see Example 4(b)), 29 µl of 12 M NaOH, reaction time 23 h. Recrystallization from ether/*n*-pentane (1/1) afforded 65 mg (73.4%); colorless crystals, m.p.: 100-105 °C (decomposition). The analytical data of the compound is in agreement with that of the (*S*)-enantiomer **S-37.** $[\alpha]_D^{20} = +13.4$ (c = 1.57, $CHCl_3$).

Further compounds according to the present invention were prepared as illustrated in Reaction Scheme 9. The reactions are explained in more detail in the following working examples.

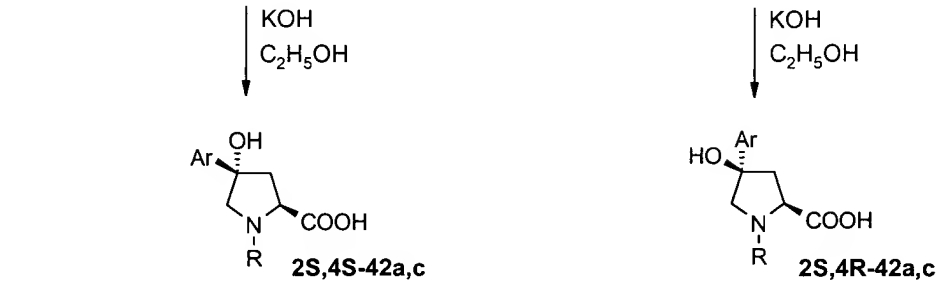
Reaction Scheme 9



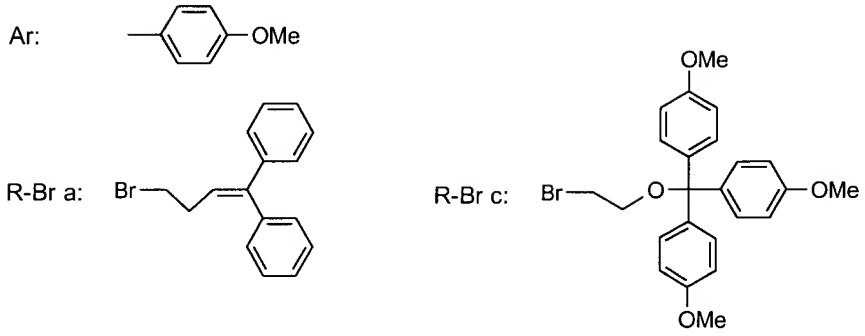
2S,4R-38-HCl **2S,4R-39a,c** **S-40a,c**

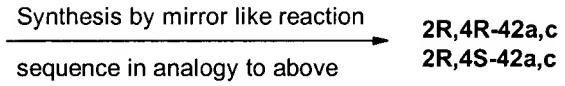


2S,4S-41a,c **2S,4R-41a,c**



2S,4S-42a,c **2S,4R-42a,c**



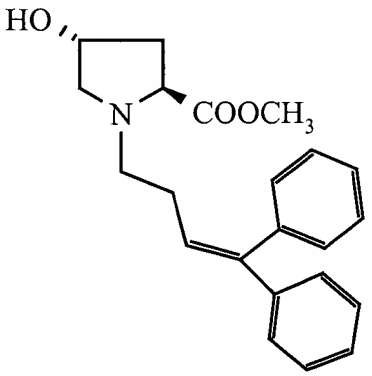


2R,4R-42a,c
2R,4S-42a,c

(2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic acid methyl ester hydrochloride (2S,4R-38-HCl)

Synthesis starting from 4.50 g (34.3 mmol) of (2*S*,4*R*) 4-hydroxypyrrolidine-2-carboxylic acid according to S.C. Mayer, J. Ramanjulu, M.D. Vera, A.J. Pfizenmayer, M.M. Joullie, *J. Org. Chem.* **1994**, 59, 5192-5205. Yield 5.50 g (96%). M.p.: 168-171°C (lit. 168-170°C), $[\alpha]_D^{20}$ = -21.3° (c = 1.0, CH_3OH), (lit. -19.5°, c = 1, CH_3OH).

(2*S*,4*R*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxypyrrolidine-2-carboxylic acid methyl ester (2S,4R-39a)

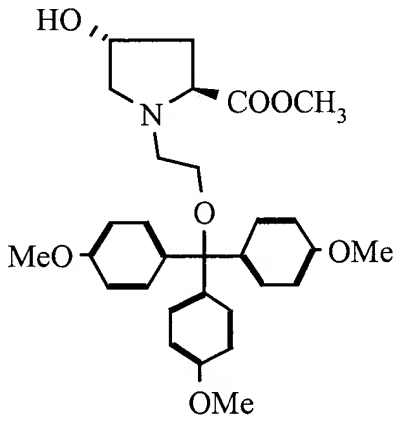


2S,4R-39a

50 mg (0.30 mmol) of potassium iodide and 454 mg (1.50 mmol) of 4,4-diphenylbut-3-en-1-yl bromide were added to a mixture of 274 mg (1.0 mmol) of **2S,4R-38-HCl** and 691 mg (5.0 mmol) of potassium carbonate in 8 ml of acetonitrile. The mixture was stirred at room temperature for 144 h. Inorganic salts were removed by filtration. The filtrate was concentrated, leaving a yellow oil. Purification by column chromatography (heptane/acetone = 4/1) afforded 277 mg (52 %) of a colorless oil.

^{1}H NMR($CDCl_3$): δ = 2.03 (ddd, *J* = 13.4/7.8/3.1 Hz, 1 H, C*H*$_2$CHCOO), 2.15-2.22 (m, 1 H, C*H*$_2$CHCOO), 2.30 (pseudo-q, *J* = 7.6 Hz, 2 H, =CHC*H*$_2$), 2.41 (dd, *J* = 10.1/3.6 Hz, 1 H, NC*H*$_2$CHO), 2.62 (dt, *J* = 12.2/7.5 Hz, 1 H, NC*H*$_2$CH$_2$), 2.82 (dt, *J* = 12.2/7.7 Hz, 1 H, NC*H*$_2$CH$_2$), 3.33 (dd, *J* = 10.1/5.5 Hz, 1 H, NC*H*$_2$CHO), 3.53 (t, *J* = 7.7 Hz, 1 H, NCHCOO), 3.67 (s, 3 H, $COOCH_3$), 4.40-4.45 (m, 1 H, C*H*OH), 6.07 (t, *J* = 7.3 Hz, 1 H, =C*H*CH$_2$), 7.15-7.38 (m, 10 H, aromat. H).

(2*S*,4*R*)-4-Hydroxy-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2- carboxylic acid methyl ester (2S,4R-39c)



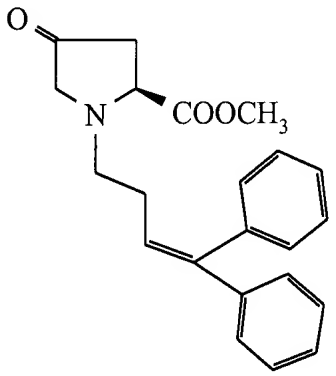
2S,4R-39c

A mixture of 273 mg (1.49 mmol) of **(2S,4R-38-HCl)**, 682 mg (1.49 mmol) of 2-[(trismethoxyphenyl)]methoxy]ethyl bromide, 680 mg (6.85 mmol) of potassium carbonate and 50 mg (0.3 mmol) of potassium iodide was stirred at room temperatue for 9 days. Following filtration and concentration the crude product was purified by column chromatography (alumina, pH 7.5, mesh 70-230, heptane/acetone = 2/1), thereby obtaining 414 mg (53%) of a colorless oil.

$[\alpha]_D^{22}$ = -24.5° (c = 0.55, ethanol). - ^{1}H NMR ($CDCl_3$): δ = 2.00-2.07 (m, 1 H, C*H*$_2$CHCOO), 2.12-2.19 (m, 1 H, C*H*$_2$CHCOO), 2.57 (dd, *J* = 10.2/3.4 Hz, 1 H, NC*H*$_2$CHO), 2.79-2.86 (m, 1 H, NC*H*$_2$CH$_2$), 2.91-2.98 (m, 1 H, NC*H*$_2$CH$_2$), 3. (20 (t, *J* =

6.1 Hz, 2 H, NCH_2CH_2), 3.38 dd, J = 10.2/5.4 Hz, 1 H, NCH_2CHO), 3.64-3.66 (m, 1 H, NCHCOO), 3.65 (s, 3 H, $COOCH_3$), 3.78 (s, 9 H, Ar-OCH_3), 4.35-4.45 (m, 1 H, CHOH), 6.83-6.79 (m, 6 H, 3′-H Ar_3CO), 7.29-7.33 (m, 6 H, 2′-H Ar_3CO).

(2*S*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-oxopyrrolidine-2- carboxylic acid methyl ester (S-40a)

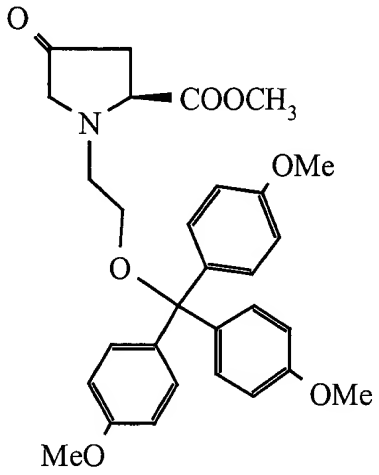


S-40a

193 mg (1.455 mmol) of oxalyl chloride was added to a solution of 227 mg (2.91 mmol) of DMSO in 4.5 ml of dichloromethane at –78 °C within 5 min. After 15 min, 357 mg (0.97 mmol) of **2S,4R-39a** in 1.5 ml of dichloromethane were added at –78°C. Thereafter the reaction mixture was stirred for 30 min at –70 - –60°C. Following the addition of triethylamine (0.334 ml, 2.4 mmol) the temperatue was held at –70 - –60°C for additional 15 min and then the mixture was slowly heated to room temperature and stirred for additional 15 min. The mixture was poured into a two-phase system consisting of 10 ml of dichloromethane, 15 ml of water and 3.7 ml of 0.85 M aqueous potassium hydroxide solution. The organic phase was washed with water, dried over sodium sulfate and concentrated, leaving an oil which upon purification by column chromatography (heptane/acetone = 4/1) afforded 312 mg (87%) of a colorless oil. $[\alpha]_D^{25}$ = -32.4° (c = 1.255, ethanol). - ^{1}H NMR ($CDCl_3$): δ = 2.26 (pseudo-q, J = 7.3 Hz, 2 H, $=CHCH_2CH_2$), 2.43 (dd, J = 17.9/5.5 Hz, 1 H, CH_2CHCOO), 2.54-2.62 (m, 2 H, CH_2CHCOO and NCH_2CH_2), 2.77 (dt, J = 12/7 Hz, 1 H, NCH_2CH_2), 2.91 (d, J = 17.2 Hz, 1 H, NCH_2CO),

3.29 (d, J = 17.2 Hz, 1 H, NCH_2CO), 3. 65 (s, 3 H, COOCH_3), 3.70 (dd, J = 7.8/5.5 Hz, 1 H, NCHCOO), 6.02 (t, J = 7.3 Hz, 1 H, =CHCH_2CH_2), 7.07-7.36 (m, 10 H, aromat. H).

(2*S*)-4-Oxo-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2- carboxylic acid methyl ester (S-40c)



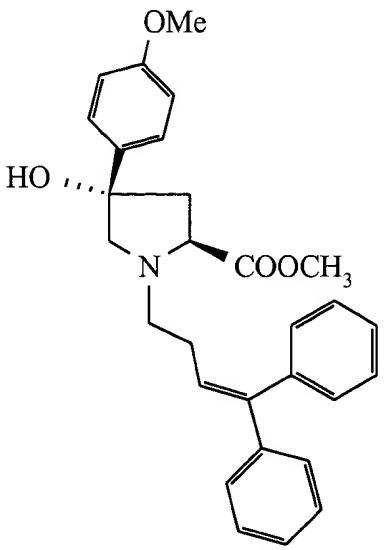
S-40c

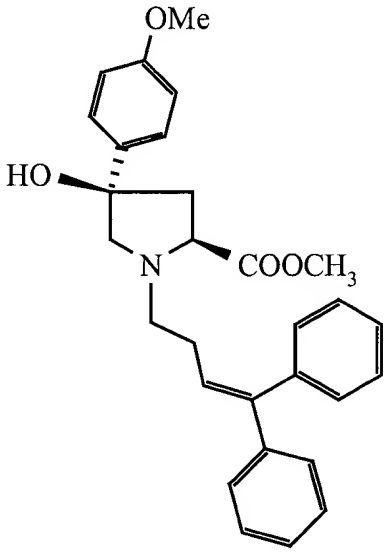
As described for **S-40a,** first 0.065 ml (0.921 mmol) of DMSO was reacted with 0.42 ml (0.461 mmol) of oxalyl chloride in dichloromethane and then there were added to the reaction mixture, at –70°C, first 160 mg (0.307 mmol) of **2S,4R-39c** and after 10 min, triethylamine (0.143 ml, 0.993 mmol). Then slow heating to room temperature was effected, whereafter stirring was continued for 15 min. Subsequently 0.85 M aqueous potassium hydroxide solution was added until the aqueous phase was in the range of pH 7-8. Following extraction with dichloromethane, drying over sodium sulfate and concentration were effected. Upon purification by column chromatography (alumina pH 7.5, heptane/ethyl acetate = 3/1) 132 mg (83%) of a highly viscous, colorless oil was isolated.

$[\alpha]_D^{29}$ = -6.4° (c = 1.83, ethyl acetate). - ^{1}H NMR ($CDCl_3$): δ = 2.48 (dd, J = 18.0/5.5 Hz, 1 H, CH_2CHCOO), 2.65 (dd, J = 18.0/7.8 Hz, 1 H, CH_2CHCOO), 2.83 (dt, J = 13.0/5.6 Hz, 1 H, NCH_2CH_2), 2.94 (dt, J = 5.6/13.0 Hz, 1 H, NCH_2CH_2), 3.13 (d, J = 17.4 Hz, 1 H, NCH_2CO), 3.24 (t, J = 5.6 Hz, 2 H, NCH$_2$CH_2), 3.44 (d, J = 17.4 Hz, 1 H,

NCH_2CO), 3.72 (s, 3 H, COOCH_3), 3.78 (s, 9 H, ArOCH_3), 3.84 (dd, J = 5.5/7.8 Hz, 1 H, NCHCOO), 6.79-6.83 (m, 6 H, 3′-H Ar_3CO), 7.29-7.32 (m, 6 H, 2′-H Ar_3CO).

(2*S*,4*S*) N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy–4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid methyl ester (2S,4S-41a) and
(2*S*,4*R*) N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy-4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid methyl ester (2S,4R-41a)





2S,4S-41a **2S,4R-41a**

Method A:

To 145 mg (0.415 mmol) of **S-40a** in 10 ml of ether there was added, at -75°C, 1 ml of a 0.74 M solution of 4-methoxyphenylmagnesium bromide in ether. After 4 h at –75 °C the reaction was stopped by adding saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether. The combined ethereal phases were dried over sodium sulfate and concentrated. Analysis by HPLC (column A see p.18, heptane/ethyl acetate = 70/30) of the mixture of diastereomers indicated a ratio of 96/4. Through purification by column chromatography (heptane/ethyl

acetate = 3/1) 104 mg (55 %) of the mixture of diastereomers and 13 mg of starting material **S-40a** were obtained.

Method B:

215 mg (0.875 mmol) of anhydrous cerium(III) chloride was dried in vacuo for 15 min at 140°C. Upon cooling to 0°C, 5 ml of a 0.76 M solution of 4-methoxyphenylmagnesium bromide (0.77 ml, 0.584 mmol) in THF was added. After stirring for one hour, the suspension was brought to –60°C and added to a solution of 120 mg (0.343 mmol) of **S-40a** in 3 ml of THF at –60°C. After 15 h the reaction was stopped at –60°C by adding saturated ammonium chloride solution. Analysis by HPLC (column A, heptane/ethyl acetate = 70/30) of the mixture of diastereomers indicated a ratio of 40/60. Upon purification by column chromatography (heptane/ethyl acetate = 3/1) 68 mg (43 %) of the mixture of diastereomers was obtained.

Method C:

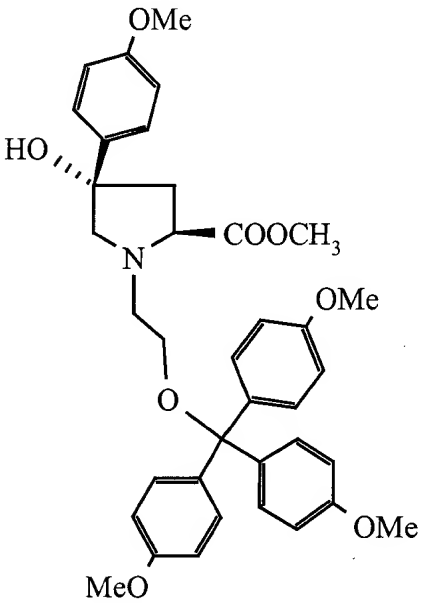
Conditions as for Method B, with the exception that the reaction was conducted at 0°C. Ratio of the diastereomers according to HPLC analysis (column A, heptane/ethyl acetate = 70/30) 48/52.

The predominant diastereomer could be prepared in pure form by recrystallization of the mixture of diastereomers obtained by Method A from diisopropyl ether. Colorless crystals, yield 72 mg (38 %), m.p.: 97-98°C. $[\alpha]_D^{20}$ = -4.4°C (c = 1.01, $CHCl_3$). - ^1H NMR ($CDCl_3$): δ = 2.26 (pseudo-q, *J* = 7.5 Hz, 2 H, NCH_2CH_2), 2.33 (d, *J* = 7.7 Hz, 2 H, CH_2CHCOO), 2.70 (dt, *J* = 12.0/7.7 Hz, 1 H, NCH_2CH_2), 2.73 (d, *J* = 10.3 Hz, 1 H, NCH_2CO), 2.84 (dt, *J* = 12.0/7.7 Hz, 1 H, NCH_2CH_2), 3.34 (d, *J* = 10.3 Hz, 1 H, NCH_2CO), 3.62 (s, 3 H, Ar-OCH_3), 3.71 (s, 3 H, $COOCH_3$), 3.77 (t, *J* = 7.7 Hz, 1 H, NCHCOO), 6.04 (t, *J* = 7.3 Hz, 1 H, $=CHCH_2CH_2$), 6.75-6.80 (m, 2 H, 3`-H *Ar*COH), 7.08- 7.36 (m, 12 H, 2`-H of *Ar*COH and $=CPh_2$).

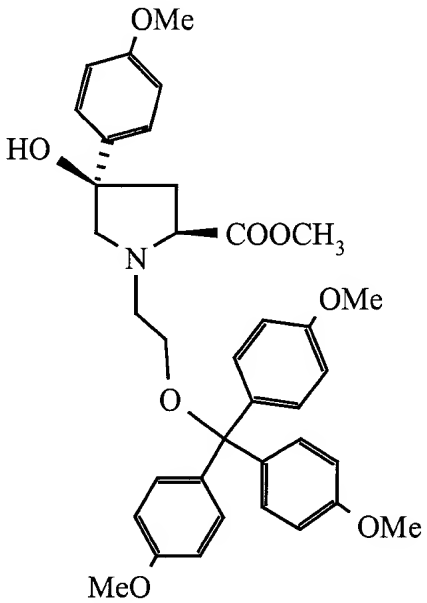
The minor diastereomer could be isolated in pure form by recrystallization of the mixture

of diastereomers obtained by Method B from diisopropyl ether. Colorless crystals, m.p.: 94-96°C. $[\alpha]_D^{20}$ = – 49.4° (c = 0.815, $CHCl_3$). - ^{1}H NMR ($CDCl_3$): δ = 2.15 (ddd, *J* = 13.9/3.2/2.0 Hz, 1 H, C*H*2CHCOO), 2.25 (pseudo-q, *J* = 7.7/7.3 Hz, 2 H, NCH2C*H*2), 2.49 (dd, *J* = 13.9/10.7 Hz, 1 H, C*H*2CHCOO), 2.63-2.70 (m, 1 H, NC*H*2CH2), 2.66 (d, *J* = 9.2 Hz, 1 H, NC*H*2CO), 2.80 (dt, *J* = 7.7/12.1 Hz, 1 H, NC*H*2CH2), 3.09 (dd, *J* = 9.2/1.9 Hz, 1 H, NCH_2CO), 3.44 (dd, *J* = 10.7/3.2 Hz, 1 H, NCHCOO), 3.66 (s, 3 H, Ar-OC*H*3), 3.72 (s, 3 H, COOCH3), 3.92 (s, 1 H, OH), 6.05 (t, *J* = 7.3 Hz, 1 H, =C*H*CH2), 6.78-6.81 (m, 2 H, 3`-H *Ar*COH), 7.09-7.33 (m, 12 H, 2´-H of *Ar*COH, and =C*Ph*$_2$).

(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl) methoxy]ethyl}-pyrrolidine-2-carboxylic acid methyl ester (2S,4S-41c) and (2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl) methoxy]ethyl}-pyrrolidine-2-carboxylic acid methyl ester (2S,4R-41c)



2S,4S-41c



2S,4R-41c

Method A:

To 251 mg (0.483 mmol) of **S-40c** in 20 ml of ether there was added, at –60 °C, 0.68 ml of a 0.833 M solution of 4-methoxyphenylmagnesium bromide in ether. After 20 h at -60°C the reaction was stopped by saturated ammonium chloride solution. The organic phase was separated and the aqueous phase was extracted with ether. The combined ethereal phases were dried over sodium sulfate and concentrated. Analysis by HPLC (column A, heptane/ethyl acetate = 60 / 40) of the mixture of diastereomers indicated a ratio of 90/10. Upon purification by column chromatography (alumina, pH 7.5, heptane/acetone = 3/2) 104 mg (34 %) of the mixture of diastereomers and 98 mg of the starting material **S-40c** were obtained.

Method B:

To 130 mg (0.527 mmol) of anhydrous cerium(III) chloride, dried in vacuo at 130-140 °C, there were added, at 0°C, 5 ml of THF and 0.80 ml of a 0.67 M solution of 4-methoxyphenylmagnesium bromide (0.528 mol) in THF. After stirring for one hour, the suspension was cooled to –60°C and added to a mixture of 196 mg (0.377 mmol) of **S-40c** in 6 ml of THF at –60°C. After 19.5 h the reaction was stopped at –60°C by adding saturated ammonium chloride solution. The organic phase was isolated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over magnesium sulfate and concentrated, leaving a yellow oil. Analysis by HPLC (column A, heptane/ethyl acetate = 60/40) of the mixture of diastereomers indicated a ration of 1/1. Upon purification by column chromatography (heptane/ethyl acetate = 3/2), 142 mg (60 %) of the mixture of diastereomers was obtained. The mixture of diastereomers was resolved by preparative HPLC (heptane/ethyl acetate = 55/45).

Predominant diastereomer: Yield: 57 mg (24%), highly viscous, colorless oil. $[\alpha]_D^{20}$ = -7.1° (c = 1.10, acetone). – ^{1}H NMR ($CDCl_3$): δ = 2.35-2.42 (m, 2 H, CH_2CHCOO), 2.54 (s, 1 H, OH), 2.96 (d, J = 10.7 Hz, 1 H, NCH_2CO), 2.92-3.00 (m, 1 H, NCH_2CH_2), 3.07 (dt, J = 12.9/5.9 Hz, 1 H, NCH_2CH_2), 3.18-3.25 (m, 2 H, NCH_2CH_2O), 3.49 (d, J = 10.7 Hz, 1 H, NCH_2CO), 3.69 (s, 3 H, $ArOCH_3$), 3.78 (s, 9 H, $ArOCH_3$), 3.79 (s, 3 H, $COOCH_3$), 3.94 (t, J = 6 Hz, 1 H, $NCHCOO$), 6.79-6.83 (m, 6 H, 3′-H Ar_3CO), 6.85-6.88

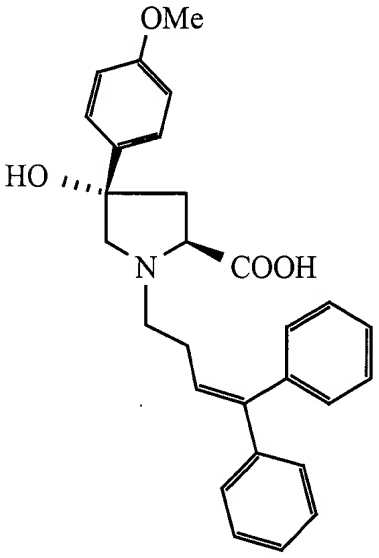
(m, 2 H, 3′-H *Ar*COH), 7.31-7.34 (m, 6 H, 2′-H Ar_3CO), 7.38-7.42 (m, 2 H, 2′-H *Ar*COH).

Minor diastereomer: Yield: 62 mg (26 %), highly viscous, colorless oil.

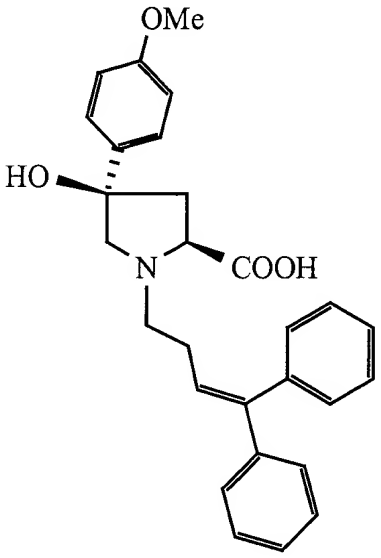
$[\alpha]_D^{20} = -18.6°$ (c = 0.80, acetone). - ^{1}H NMR ($CDCl_3$): δ = 2.23 (ddd, J = 13.9/3/2 Hz, 1 H, CH_2CHCOO), 2.56 (dd, J = 13.9/10.8 Hz, 1 H, CH_2CHCOO), 2.89 (d, J = 9.2 Hz, 1 H, NCH_2CO), 2.87-2.96 (m, 1 H, NCH_2CH_2), 2.98-3.05 (m, 1 H, NCH_2CH_2), 3.21 (dd, J = 9/2 Hz, 1 H, NCH_2CO), 3.20-3.25 (m, 2 H, NCH_2CH_2O), 3.63 (dd, J = 10.8/3.2 Hz, 1 H, NCHCOO), 3.71 (s, 3 H, $COOCH_3$), 3.79 (s, 9 H, $ArOCH_3$), 3.81 (s, 3 H, $ArOCH_3$), 6.81-6.84 (m, 6 H, 3′-H Ar_3CO), 6.86-6.90 (m, 2 H, 3′-H *Ar*COH), 7.31-7.35 (m, 6 H, 2′-H Ar_3CO), 7.37-7.40 (m, 2 H, 2′-H *Ar*COH).

(2*S*,4*S*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy–4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid (2S,4S-42a) and

(2*S*,4*R*)-N-(4,4-Diphenylbut-3-en-1-yl)-4-hydroxy–4-(4-methoxyphenyl)-pyrrolidine-2- carboxylic acid (2S,4R-42a)



2S,4S-42a



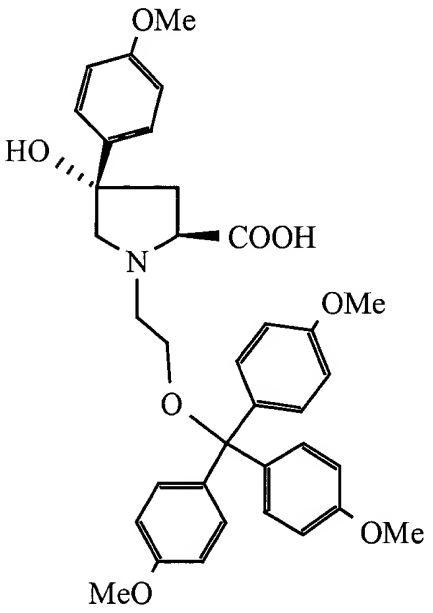
2S,4R-42a

Following the addition of 0.386 ml of 0.85 M aqueous potassium hydroxide solution, 50 mg (0.109 mmol) of the predominant diastereomer of **2S,4S-41a/2S,4R-41a (Method A)** in 1.7 ml of ethanol was stirred for one hour at room temperature. Subsequently 0.3 ml of 1 M hydrochloric acid was added to adjust the pH to 6-7 and 1.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter carefull concentration in vacuo (T < 30°C) was carried out. The residue was additioned with water and filtered. The solid obtained upon filtration was dried in air and subsequently purified by column chromatography (diisopropyl ether → ethanol gradient). This afforded 36 mg (74%) of colorless crystals, m.p.: 173-175°C. $[\alpha]_D^{20}$ = -28.0° (c = 0.64, methanol). – ^{1}H NMR (CD_3OD): δ = 2.42 (dd, J = 13.3/12.1 Hz, 1 H, CH_2CHCOO), 2.57 (pseudo-q, J = 7.6

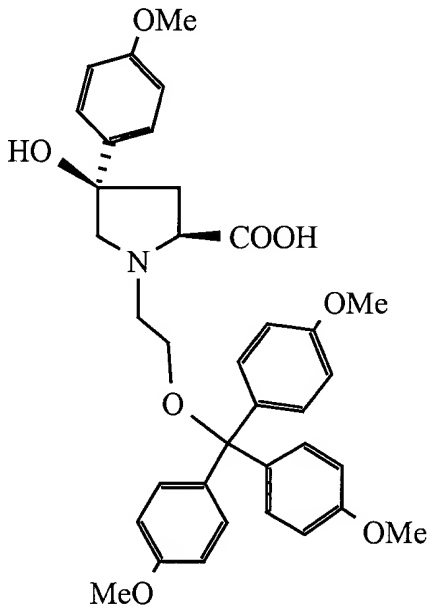
Hz, 2 H, NCH_2CH_2), 2.65 (ddd, J = 13.3/6.7/2.1 Hz, 1 H, CH_2CHCOO), 3.26-3.33 (m, 1 H, NCH_2CO), 3.33-3.40 (m, 1 H, NCH_2CH_2), 3.54 (dt, J = 12.3/8.0 Hz, 1 H, NCH_2CH_2), 3.68 (d, J = 12.3 Hz, 1 H, NCH_2CO), 3.78 (s, 3 H, $ArOCH_3$), 4.25 (dd, J = 12.1/6.7 Hz, 1 H, NCHCOO), 6.12 (t, J = 7.4 Hz, 1 H, $=CHCH_2$), 6.90-6.93 (m, 2 H, 3′-H *Ar*COH), 7.17-7.44 (m, 12 H, 2′-H *Ar*COH and $=CPh_2$).

Following the addition of 0.154 ml of a 0.85 M aqueous solution of potassium hydroxide, 20 mg (0.0437 mmol) of the minor diastereomer of **2S,4S-41a/2S,4R-41a (Method A)** in 0.6 ml of ethanol was stirred at room temperature for 1 h. Thereafter the pH was adjusted to 6-7 with 1 M hydrochloric acid, and 0.6 ml of 0.2 M phosphate buffer (pH 5.5) was added to the mixture. Thereafter careful concentration in vacuo was carried out (T < 30°C). The residue was purified by column chromatography (diisopropyl ether → ethanol gradient) and afforded 17 mg (88 %) as yellowish crystals, m.p.: 168-173°C. $[\alpha]_D^{20}$ = -35.7° (c = 0.585, $CHCl_3$). - ^{1}H NMR (CD_3OD): δ = 2.53 (d, J = 13.5 Hz, 1 H, CH_2CHCOO), 2.57-2.65 (m, 2 H, NCH_2CH_2), 2.85 (dd, J = 13.5/11.4, 1 H, CH_2CHCOO), 3.25 (d, J = 11.0 Hz, 1 H, NCH_2CO), 3.25-3.35, 3.42-3.46 (m, 3 H, NCH_2CO and NCH_2CH_2), 3.78 (s, 3 H, $ArOCH_3$), 4.00-4.02 (m, 1 H, NCHCOO), 6.11 (dd, 1 H, J = 6.6/8.4 Hz, $CH_2CH_2CH=$), 6.89-6.92 (m, 2 H, 3′-H *Ar*COH), 7.23-7.42 (m, 12 H, 2′-H *Ar*COH and $=CPh_2$)

(2*S*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid (2S,4S-42c) and (2*S*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-N-{2-[tris(4-methoxyphenyl)methoxy]ethyl}-pyrrolidine-2-carboxylic acid (2S,4R-42c)



2S,4S-42c



2S,4R-42c

Following the addition of 0.39 ml of a 0.85 M aqueous solution of potassium hydroxide, 30 mg (0.0988 mmol) of the predominant diastereomer of **2S,4S-41c/2S,4R-41c (Method A)** in 1.0 ml of ethanol was stirred at room temperature for 105 min. Subsequently the pH was adjusted to 7-8 with 0.35 ml of 1 M hydrochloric acid, and 1.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter careful concentration in vacuo was carried out (T < 25°C). The residue was washed with water and dried in vacuo. Yield: 26 mg (89%); colorless crystals, m.p.: 138-139°C.

$[\alpha]_D^{20}$ = -3.9° (c = 0.85, methanol). - ^{1}H NMR (CD_3OD): δ = 2.32 (dd, *J* = 13.3/11.6 Hz, 1 H, C*H*$_2$CHCOO), 2.57 (ddd, *J* = 13.3/7.1/2.1 Hz, 1 H, C*H*$_2$CHCOO), 3.14 (dd, *J* = 12.5/2.1 Hz, 1 H, NC*H*$_2$CO), 3.32-3.41 (m, 2 H, NCH$_2$C*H*$_2$), 3.37 (d, *J* = 12.5 Hz, 1 H, NC*H*$_2$CO), 3.44-3.54 (m, 2 H, NC*H*$_2$CH$_2$), 3.63 (s, 9 H, ArOC*H*$_3$), 3.70 (s, 3 H,

ArOCH_3), 4.29 (dd, J = 11.6/7.1 Hz, 1 H, NCHCOO), 6.73-6.76 (m, 6 H, 3′-H Ar_3CO), 6.78-6.81 (m, 2 H, 3′-H ArCOH), 7.23-7.26 (m, 8 H, 2′-H ArCOH and Ar_3CO).

Following the addition of 0.465 ml of a 0.85 M aqueous potassium hydroxide solution, 62 mg (0.0988 mmol) of the minor diastereomer of **2S,4S-41c/2S,4R-41c (Method A)** in 2.0 ml of ethanol was stirred at room temperature for 3.5 h. Subsequently the pH was adjusted to 7-8 with 0.35 ml of 1 M hydrochloric acid, and 2.0 ml of 0.2 M phosphate buffer (pH 6.6) was added to the mixture. Thereafter carefull concentration in vacuo was carried out (T < 25°C). The residue was washed with water and dried in vacuo. This afforded 54 mg (89 %) of colorless crystals, m.p.: 105-108°C.

$[\alpha]_D^{20}$ = +1.5° (c = 1.15, methanol). - ^{1}H NMR (CD_3OD): δ = 2.46-2.50 (d, broadened, J = 13.5 Hz, 1 H, CH_2CHCOO), 2.75 (dd, J = 13.5/11.5, 1 H, CH_2CHCOO), 3.05-3.14 (m, 2 H, NCH_2CO), 3.25-3.32 (m, 2 H, NCH_2CH_2), 3.49-3.62 (m, 2 H, NCH_2CH_2), 3.67 (s, 9 H, ArOCH_3), 3.70 (s, 3 H, ArOCH_3), 4.06 (dd, J = 11.5/2 Hz, 1 H, NCHCOO), 6.77-6.84 (m, 8 H, 3′-H ArCOH and Ar_3CO), 7.22-7.25 (m, 2 H, 2′-H ArCOH), 7.28-7.32 (m, 6 H, 2′-H Ar_3CO).